CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75288

CORRESPONDENCE

ANDA 75-288

SCS Pharmaceuticals
Attention: Doranne Frano
4901 Searle Parkway
Skokie IL 60077

FEB 6 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Norgestrel and Ethinyl Estradiol Tablets USP, 0.3 mg/0.03 mg, 21 and 28 day

DATE OF APPLICATION: December 24, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 29, 1997

We also acknowledge your correspondence dated January 30, 1998.

We will correspond with you further after we have had the opportunity to review your application.

In the interim, please submit a diskette in ASCII format containing pharmacokinetic data and the model codes used in statistical analyses. For each study, two separate files should be configured as follows:

(a) subj seq trt per AUC_{0-t} AUC_{inf} (Where applicable) C_{max} T_{max} K_{el} and $t_{1/2}$;...

(b) subj seq per trt C_1 C_2 C_3.....C_n,

where C is the concentration at various sampling times. Fields should be delimited by one blank space and each missing value should be denoted by a period (.).

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Sheila O'Keefe
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-288
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-330
HFD-600/Reading File
HFD-610/J.Phillips
HFD-615/MBennett

Endorsements: HFD-615/PRickman, Chief, RSB date 2/5/98
HFD-615/SMiddleton, CSO date 2/2/98
HFD-625/MSmela, Sup. Chemistry/ date

ANDA Acknowledgment Letter!

SEARLE

SEARLE
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FAX (847) 982-4701

June 10, 1999

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NDA ORIG AMENDMENT
N/FA

RE: ANDA 75-288
Low-Ogestrel 21 & 28
(norgestrel and ethinyl estradiol
Tablets USP, 0.3/0.03 mg)
TELEPHONE AMENDMENT

Dear Mr. Sporn:

Per a telephone request from Dr. Cai, SCS Pharmaceuticals hereby amends the above mentioned ANDA with a revised stability commitment (document no. 2559-NGE-NC-02a, 10, June 1999).

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (fax)

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CDER
EVALUATION AND RESEARCH

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May 27, 1999

NEW CORRESP

NC 10 Fax

Douglas Sporn, MD
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation
and Research (HFD-600)
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 75-288
Low-Ogestrel 21 and 28
(norgestrel and ethinyl estradiol tablets
USP 0.3/0.03 mg)
FACSIMILE AMENDMENT

Dear Mr. Sporn:

In response to your fax of May 13, 1999, SCS Pharmaceuticals hereby amends the above mentioned ANDA.

Your comments are listed below in italics, followed by our response.

CHEMISTRY MANUFACTURING AND CONTROLS:

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

   The % overage of ethinyl estradiol has been removed. The revised batch record is provided in Attachment 1. A revised components and composition page (document number 2533-NGE-DA-02, 20 May 1999) is provided in Attachment 2.

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

   The Drug Substance Specification for Ethinyl Estradiol has been revised to include the USP test for "Completeness of Solution". The revised specification (document number 2532-ETE-KA-01, 13 May 1999) is provided in Attachment 3.

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

   Limit (range) for individual tablet weight.

   Specifications for

   Sample Size: 1-3 dosage units equivalent;

   Acceptance Criteria: Mean of 90.0-110.0% with RSD no more than % for both active ingredients.

   The Master Batch Record has been revised to incorporate a limit for individual tablet weight. A specification has been added to the In Process Controls document (document number 3048-NGE-DJ-01, 20 May 1999) provided in Attachment 4. The Master Batch record has been modified to incorporate the collection of the sample. The test is performed per SOP. A copy of the revised Master Batch Record is provided in attachment 1.

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

   A maximum drying time for granulation has been added into the Master Batch Record as requested (Attachment 1).

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.

   The aluminum foil supplier for the marketed product will be

   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

   SCS Pharmaceuticals requests the withdrawal, from this application, of as a vendor for aluminum foil. A Revised Packaging Component Manufacturers document (document number 2525-PKG-EY-01, 14 May 1999) is provided in Attachment 5.

   If you choose to use the C/C system using the aluminum from 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.

   Moisture Permeation Testing for PVC/Aclar/Aluminum Foil Blister (document number 3297-NGE-KF-01, 25 May 1999) is provided in Attachment 6.

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

   The test product should meet the following specifications:

   The dissolution testing has been revised as requested. A revised Norgestrel and Ethinyl Estradiol Tablets Specification (document number 2535-NGE-KQ-02, 20 May 1999) is provided in Attachment 7.

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.*

   Based on the impurity data obtained on this product, a limit for any unidentified individual impurity of NMT % of the label claim at release and NMT % at expiry have been incorporated into the finished product specification (document number 2535-NGE-KQ-02, 20 May 1999) provided in Attachment 7.

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

   The stability storage condition for active and placebo tables has been revised to The revised Stability Commitment for Low-Ogestrel Tablets (document number 2559-NGE-NC-02a, 13 May 1999), Stability Commitment for Placebo Tablets (document number 3019-PLB-NC-02a, 13 May 1999) and the Stability Protocol (document number 2560-NGE-ND-02, 26 May 1999) are provided in Attachment 8.

9. *Please provide any additional stability data if available.*

   Additional stability data for the Low-Ogestrel tablets and the placebo tablets are provided in Attachment 9.

LABELING:

1. *BLISTER CARD (21 DAY AND 28 DAY)*

   a. *Revised the established name to read as follows:*

      Norgestrel and Ethinyl Estradiol Tablets USP, 0.3 mg/0.03 mg

The established name (norgestrel and ethinyl estradiol tablets USP, 0.03 mg/0.03mg) appears as requested on the blister card. The presentation in lower case is representative of scientific and company style of displaying the generic (established) name. In addition, the contents (each white tablet (21) contains Norgestrel 0.3 mg and Ethinyl Estradiol 0.03mg) is printed on the back of the blister.

b. *Relocate the following sentence from the back panel to the front panel on your 28 day package:*

TAKE ALL WHITE TABLETS BEFORE TAKING ANY PEACH TABLETS.

The sentence "TAKE ALL REMAINING WHITE TABLETS BEFORE TAKING COLORED TABLETS" has been relocated to the front panel of the 28 day package.

2. *CARTON (6 X 21 AND 6 X 28)*

a. *Revised the established name to read as follows:*

Norgestrel and Ethinyl Estradiol Tablets USP, 0.3 mg/0.03 mg

See response 1.a.

b. *Include the following statement on your carton:*

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

The carton text for Low-Ogestel is identical to the approved cartons for the Searle innovator products Norinyl, Brevicon, Tri-Norinyl and Demulen. The cartons are provided as a secondary packaging configuration and are not dispensed to the patient. The cartons contain an "Important Note" directing the pharmacist to read the enclosed product information and to dispense Low-Ogestrel with a Brief Summary and the Detailed Patient Labeling enclosed within the tablet dispenser. Each labeling piece dispensed to the patient, has the bolded HIV statement which is printed on the front of the patient labeling. Since the carton is not dispensed to the patient and the labeling, (physician, pharmacist and patient), clearly indicates the HIV warning for the user, it is not felt necessary to include the HIV statement on the carton. However, the HIV statement will be added to the cartons and implemented on the production lots distributed after the initial launch (3 lots). A draft 28 day carton is included in Attachment 10. Only the 28 day product is planned to be distributed after initial launch.

3. *INSERT*

a. GENERAL COMMENT

i. We acknowledge your comments regarding the labeling submitted being identical in format and content to the "Searle Norinyl 1+35" product labeling (revised July 15, 1993). However, the most recent labeling was approved August 30, 1995; Revised April 1995. Therefore, you must revise your labeling to be in accord with the latest approved labeling for Norinyl 1+35.

The labeling as submitted is in compliance with the latest approved labeling for Norinyl 1+35 approved August 30, 1995. As shown in the side by side labeling document submitted in the major amendment, the Low-Ogestrel labeling is identical to the Norinyl labeling currently in use (October 30, 1997). The only difference between the 1995 and 1997 version is the change in ownership (signature line and style/format) from Syntex to Searle which occurred in August 1995.

b. PHYSICIAN LABELING

i. TITLE

We encourage the inclusion of "Rx only" in this section.

The Rx Only statement currently appears in the How Supplied section and at the end of the Physician insert. However, Rx Only will be added to the title section of the physician insert at next printing.

ii. DESCRIPTION

Revise the first two paragraphs to read as follows:

Low-Ogestrel® 0.3/30-21 Tablets (Norgestrel and Ethinyl Estradiol Tablets, USP) provide an oral contraceptive regimen consisting of 21 white tablets.

Low-Ogestrel® 0.3/30-28 Tablets (Norgestrel and Ethinyl Estradiol Tablets, USP) provide an oral contraceptive regimen consisting of 21 white tablets followed by 7 peach tablets.

The Brand Name followed by the Established Name is a consistent presentation and is in accordance with 21 CFR 201.10(g). Also see response 1.a.

iii. INDICATION AND USAGE

Low-Ogestrel® (Norgestrel and Ethinyl Estradiol Tablets USP) tablets are indicated...

See response b. ii.

Please note that WATSONPHARMA will be distributing this product upon approval. Final printed Labeling (12 copies) reflecting WATSONPHARMA as the distributor is provided in Attachment 11. Also provided is FPL (carton and blister) for a physician sample. A highlighted copy of the changes made (WATSONPHARMA Signature line) to reflect WATSONPHARMA as the distributor is provided in attachment 12.

BIOEQUIVALENCY:

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The recommended dissolution testing has been incorporated into the stability and quality control program. The revised specification (document number 2535-NGE-KQ-02, 20 May 1999) is provided in Attachment 7.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
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SEARLE

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October 16, 1998

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 75-288
Low-Ogestrel 21 and 28 day tablets
(norgestrel and ethinyl estradiol tablets USP, 0.3mg/0.03mg)
MAJOR AMENDMENT TO A PENDING APPLICATION

Dear Mr. Sporn:

In accordance with 21 CFR 314.120 and in response to your letter of July 14, 1998, SCS Pharmaceutical hereby amends the above mentioned ANDA.

Your comments are listed below in italics, followed by our response.

Chemistry Manufacturing and Controls:

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

   The % overage for the ethinyl estradiol was added to compensate for a potential loss in the manufacturing process. The process validations data will determine if the overage is necessary. Upon completion of process validation Searle will remove the % overage if it is not necessary.

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

   The specification for Norgestrel has been updated as described in USP 23, Supplement 8. A copy is provided in attachment 1.

3. *Please update your specification for Lactose Monohydrate and Purified Water to current USP 23, Supplement 8.*

   The specifications for Lactose Monohydrate and Purified Water have been updated as described in USP 23, Supplement 8. Copies have been provided in attachments 2 and 3 respectively.

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

The Microcrystalline Cellulose was tested in accordance with the then current (May 1996) USP/Supplement 4. The microcrystalline cellulose was found to meet those USP requirements. Any future testing of this or any other excipient will be in accordance with the current USP and supplements.

The specification for Microcrystalline Cellulose has been updated as described in USP 23, Supplement 7. A copy is provided in attachment 4.

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 in their COA, you must run this test for every lot.*

The specification for lactose anhydrous has been updated to current USP 23/Supplement 8, a copy is provided in attachment 5.

Since lactose anhydrous is only used in the placebo tablet, dissolution is not performed. Because dissolution is not required, testing of lactose does not seem applicable.

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

An interim cg/minute has been established. This will be confirmed during validation and then added to the batch record.

7. *We believe that in order 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.*

is adequately tested during process validation to assure uniformity on a batch to batch basis. A assay test has been added and will be performed on every batch, to confirm uniformity on a batch to batch basis. The specification is included in attachment 6.

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

Individual tablet weight is routinely collected as an in-process control. The data are recorded on a quality control in-process control record. A copy of the executed in-process record for Low-Ogestrel is provided in attachment 7.

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.*

The moisture permeation test results of the alternate materials were submitted in the original ANDA. The moisture permeation test results for the container/closure system used in the biobatch are not yet available, but will be available prior to marketing this packaging combination and the information will be submitted to the ANDA when available. The COA's containing the IR and pinhole test results for the container closure system used in the biobatch (Lot 002/RCT10242) are provided in attachment 8. Low Ogestrel production Lot 002/6K002, packaged into Lot PT 142-96, was assigned the clinical lot number RCT 10242. The clinical pharmacy record designating Lot 002 as clinical Lot RCT 10242, as submitted with bio response dated May 18 1998, is provided in attachment 9.

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

A summary of the in-process controls and associated methods used in the production of Low-Ogestrel is provided in attachment 10.

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

The disintegration test as required by USP has been added to the product release specification. A copy of the revised specification is provided in attachment 11. Also provided in attachment 11 is the revised test method incorporating the disintegration test.

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

The specification for related substances states that the tablets will contain not more than % of any individual related substance and not more than % total (i.e., the sum of all related substances at expiry). Related substances, determined to be degradants by Syntex, are quantitated against specific standard materials. Norgestrel related substances are quantitated against a norgestrel standard. Ethinyl estradiol related substances are quantitated against an ethinyl estradiol standard. Unknown related substances are quantitated against an ethinyl estradiol standard, which represents the worst case quantitation. All individual related substances are summed in the total. There is no compensation for amount of active in the tablet, even though the amounts differ greatly (30 mcg ethinyl estradiol, 300 mcg norgestrel).

The limits of NMT % individual and NMT % total related substances can be justified based on the drug substance compendial monographs and actual stability data from Low-Ogestrel tablet lots.

The specifications are based upon the drug substance specifications for Ethinyl Estradiol and Norgestrel from the USP, BP, and EP monographs.

Ethinyl Estradiol: NMT % of any individual related substance (BP and EP)
There is no specification for total related substances in current USP or any other compendium.

Norgestrel: NMT % of any individual related substance and NMT two individual related substances greater than % (BP and EP)
NMT % total related substances (USP)

These drug substance specifications allow up to % total related substances (note: prior to the 1997 BP addendum, the specification for total ethinyl estradiol related substances was NMT %; combining this with the corresponding specification for norgestrel yields NMT % total related substances), up to % of any individual norgestrel related substance, and up to % of any ethinyl estradiol related substance to be present in the drug substances used to formulate the drug product. Thus, the proposed drug product specifications of NMT % any individual and NMT % total related substances represent tight controls on the related substances of ethinyl estradiol and norgestrel.

Chromatographic analysis also supports these limits. Analyses of two lots of Low-Ogestrel tablets shows that individual impurities/degradation products can be present at levels of % or greater during stability. Table 1 shows data for Lot 002 and expired Lot 92119. Lot 92119 was manufactured by Syntex and was stored for approximately five years at room temperature. Lot 002 was manufactured by Searle and was stored for approximately one year at 30°C/60% relative humidity.

Table 1

Related Substances Testing Results for Two Low-Ogestrel Tablet Lots

Lot Number	% Found	% Found	Total % Related Substances Found
92119	0.9	0.8	5.4
002	less than 0.5	0.6	2.9

*EE = Ethinyl Estradiol

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.*

The specification has been revised to The Norgestrel drug substance melting range is The lower limit for Norgestrel in Low-Ogestrel Tablets will be lower than the drug substance's stated lower range. A copy of the revised specification document is provided in attachment 11.

The rationale for this specification range is based upon the melting point criteria in the USP monograph for Levonorgestrel/Ethinyl Estradiol Tablets. The monograph states that the melting point is not lower than The Levonorgestrel drug substance is stated as "between The lower value of lower than the Levonorgestrel drug substance lower limit of is to account for extractables (included in the separation of Levonorgestrel from tablet excipients) that can depress the melting point.

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

The reproducibility requirement will be changed to: "The %RSD for Ethinyl Estradiol and Norgestrel peak responses for six consecutive injections are not more than % respectively."

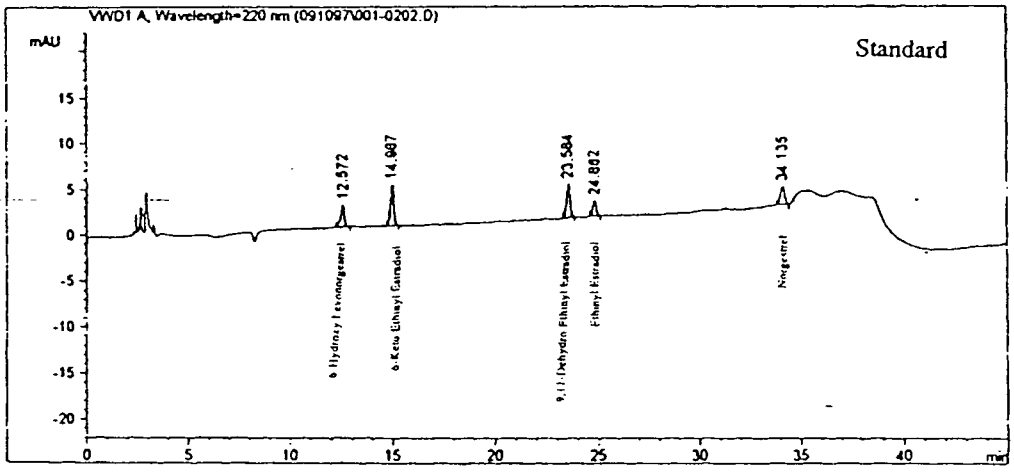
The reproducibility requirement of % RSD or less for Ethinyl Estradiol and Norgestrel was determined from method validation work performed by Syntex and documented in a report which was included in the original ANDA submission (page 970). Repeatability experiments for Ethinyl Estradiol, Levonorgestrel, and three known related substances yielded results ranging from % RSD. On page 986 of the ANDA, in the Repeatability section, Syntex states that the %RSD for each compound is not more than %.

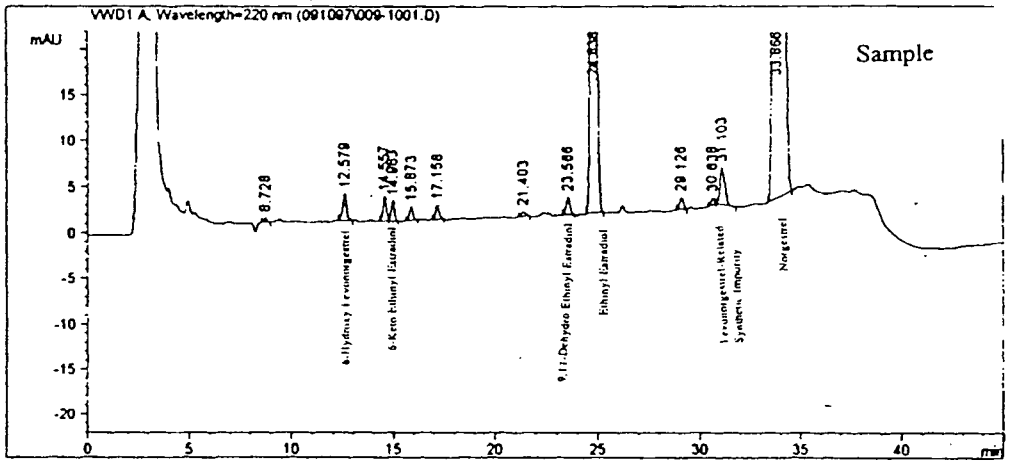
System suitability data compiled from multiple stability runs supports lowering the %RSD requirement for ethinyl estradiol, but not for norgestrel. The reproducibility of replicate standard responses ranged from % RSD for Ethinyl Estradiol and % RSD for Norgestrel.

Regarding the sensitivity of the Ethinyl Estradiol Related Substances limit of quantitation (LOQ) for the method, Low-Ogestrel tablets stability testing has demonstrated that the method is capable of detecting impurities at levels of % or less. See Figure 1. The standard preparations contain Ethinyl Estradiol, Norgestrel, and their principal related substances at their respective LOQs: Ethinyl Estradiol, %); Norgestrel and %).

Figure 1

Standard and Sample Chromatograms from the 52 Week Testing Interval for Low-Ogestrel Tablet Lot 002





Compound	Retention Time (minutes)	(Estimated*) Percent Found
	8.728	<0.5
	12.579	0.1
	14.557	0.7
	14.963	<0.5
	15.873	<0.5
	17.158	0.5
	21.403	<0.5
	23.566	0.5
	29.126	<0.5
	30.638	<0.5
	31.103	0.2

*Estimated percent found represents compounds detected below the LOQ for Ethinyl Estradiol Related Substances

On page 986 of the ANDA, the Syntex validation report contains a section entitled Discussion of Minimum Quantitation Limits. Syntex designated the LOQ for Ethinyl Estradiol related substances to be mcg/mL) and described how this determination was made using different systems. Each system exhibited different detector sensitivities and baseline noise levels. Verification of the Ethinyl Estradiol related substance LOQ was performed by two Searle analysts who obtained precision results comparable to those of Syntex. The data, generated at multiple sites by different analysts using different systems with different sensitivities, justify the Ethinyl Estradiol related substances LOQ of %.

It should also be noted that the USP definitions of LOQ and LOD represent different concentrations of a given analyte. On page 1983 of USP 23 (test <1225>), the LOQ is defined as the standard deviation of a number of blank sample response measurements, multiplied by a factor, usually 10. The definition of LOD is similar, except that the factor is 2 or 3. Therefore, there is a three- to five-fold difference between LOD and LOQ.

Justification for the Ethinyl Estradiol related substances LOQ of % is supported by the International Conference on Harmonization (ICH) guidelines. The ICH recommends an identification threshold for related substances of not more than 1.0% of total daily intake or 5 mcg, whichever is lower, for maximum daily doses of 1 mg per active or less. In the case of Low-Ogestrel tablets, which contain 30 mcg of Ethinyl Estradiol, the lower amount is 1.0% (equivalent to 0.3 mcg of Ethinyl Estradiol related substance). The LOQ of % for Ethinyl Estradiol related substances represents a specification limit lower than that recommended by ICH.

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

The Ethinyl Estradiol/Norgestrel assay method is an method based on the USP monograph for Levonorgestrel/Ethinyl Estradiol tablets. Selectivity of the method was performed and was included in the selectivity section of the method validation. Additional validation regarding specificity/selectivity under stressed conditions was performed for placebo, individual drug substance, and drug product. Five conditions were evaluated: acid, base, heat, oxidation, and light. A data summary report, "Degradation of ethinyl estradiol, Norgestrel and Low-Ogestrel Tablets and Under Stress Conditions" is provided in attachment 12. The stability assay method was found to be specific and stability-indicating for ethinyl estradiol and norgestrel in Low-Ogestrel Tablets.

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

The protocol/specification for stability testing of Low-Ogestrel is provided in attachment 13.

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

Stability data for the placebo tablets are provided in attachment 14. The placebo tablets are included in the post approval program. A stability commitment for the placebo is included in attachment 15.

In addition, G. D. Searle & Co. acknowledge the following:

1. *Please provide any additional stability data available.*

   Updated stability is provided in attachment 16.

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.*

   The Caguas facility is in compliance with CGMPs. A letter from the district recommending approval of this application is included in attachment 17.

   The active ingredient suppliers were inspected last year (in support of ANDA 74-538 Trivora) and found to be in compliance with CGMPs.

   Updated DMF letters authorizing access on behalf of SCS Pharmaceuticals are included in attachment 18.

3. *Your response must also address the labeling deficiencies.*

   The labeling deficiencies are addressed in this response.

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.*

   We understand that the USP analytical methods are considered regulatory for this product and that changes to the registered stability methods requires 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.*

   A response to the Bioequivalence letter of May 1, was submitted to the ANDA on May 19, 1998. All deficiencies were addressed. An explanation of the lot number system was provided in that response. A copy of the cover letter, the explanation and the documentation showing the assignment of the clinical lot number from production lot 002/6K002, packaged Lot PT 142-96 clinical Lot RCT 10242 is provided in attachment 9. Production Lot 002/clinical Lot RCT 10242 was used in the Bioequivalence study. The batch record, in-process and release data provided in the original ANDA are the biobatch data.

Labeling Deficiencies

1. *Blister Card (21 day and 28 day)*

   a. *Revise the established name to read as follows:*
   Norgestrel and Ethinyl Estradiol Tables USP, 0.3mg/0.03 mg

The established name has been revised as requested.

b. *Replace the "CAUTION: Federal law..." statement with the symbol "Rx only" or "Rx only". We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site, http://www.fda.gov/cder/guidance/index.htm for guidance.*

The caution statement has been replaced with the symbol "Rx only" in accordance with the guidance document dated February 1998.

c. *Revise the temperature storage recommendations to read as follows: Store between 15° - 25°...*

The storage temperature has been revised.

d. *We note you have preprinted the days of the week on your foil blister. There is no mention of the use of alternate date stickers. Therefore, this blister configuration allows only for a Sunday Start only. What plan do you have for "Day 1" starters. Please comment and/or revise.*

The blister (race track format) configuration is similar to the branded products Norinyl 1+35, 1+50, and Brevicon. The race track configuration allows a Day 1 Start to begin on any day in the package beginning in the top row by following the arrows until all tablets are used. The 28 day regimen package will instruct the patient to take all white pills first, to assure white "active" tablets are used before starting peach (placebo) tablets.

This blister pack configuration with the instructions provided is deemed adequate for Day 1 starters.

3. *Carton (6 x 21 and 6 x 28)*

a. *How many "Detailed" and "Brief Summary" inserts will accompany each carton?*

Each carton contains 6 blisters, 6 detailed patient summaries and 6 brief summaries. One detailed patient insert and one brief summary are dispensed with each blister.

b. *Include the established name in conjunction with the proprietary name as described in comment b under BLISTER CARD.*

The revised established name has been included in conjunction with the proprietary name as required.

c. *Include the product strength in conjunction with the established name.*

The product strength has been included with the established name.

d. *See comments a and b under BLISTER CARD?*

The carton has been revised accordingly.

4. *INSERT*

a. *GENERAL COMMENT*

i. *We acknowledge your comments regarding the labeling submitted being identical in format and content to the ' product labeling not yet approved by the Division of Reproductive and Urologic Drug Products". We find this unacceptable. The office of Generic Drugs cannot utilize labeling that has not been approved by the Agency. Therefore, you must revise your labeling to be in accordance with the latest approved labeling for Demulen (Approved April 20, 1994; Revised July 15, 1993).*

Since is pending FDA approval the labeling for Low-Ogestrel has been completely revised to be identical in content and format to the current Norinyl 1+35 labeling. Draft labeling modeled against the currently approved Norinyl 1+35 labeling (revised July 15, 1993), has been included for review.

ii. *The requirements of 21 CFR 201.10(g) must be met. The established name must appear in certain sections in association with the proprietary name. Please revise your labeling accordingly.*

The established name has been added where required in accordance with 21 CFR 201.10(g).

b. *PHYSICIAN LABELING*

i. *TITLE*

See GENERAL COMMENT under regarding the proposed proprietary name.

The physician labeling has been revised accordingly.

ii. *DESCRIPTION*

A) *Revise the first four paragraph to read as follows:*

Low-Ogestrel® 0.3/30-21 Tablets (Norgestrel and Ethinyl Estradiol Tablets, USP) provide an oral contraceptive regimen consisting of 21 white tablets.

Low- Ogestrel® 0.3/30-28 Tablets (Norgestrel and Ethinyl Estradiol Tablets, USP) provide an oral contraceptive regimen consisting of 21 white tablets followed by 7 peach tablets.

Each white tablet, for oral administration, contains 0.3 mg of norgestrel and 0.03 mg of ethinyl estradiol and the following inactive ingredients...

Each inactive peach tablet, for oral administration, in the 28 day regimen contains the following inactive ingredients...

The first four paragraphs have been revised as requested.

ii. *Include the molecular weight and molecular formula of each active ingredient.*

The molecular weight and molecular formula of each active ingredient has been added.

iii. Include the Chemical solubilities as listed in USP 23 for each active ingredient.

The chemical solubility of the active ingredients has been added.

iv. We note you have not submitted a components and composition statement for the inert peach tablets. Please revise accordingly.

The components and composition of the inert peach tablets was submitted in the placebo section of the ANDA. A copy is included in attachment 19.

iii. INDICATION AND USAGE

Low-Ogestrel® (Norgestrel and Ethinyl Estradiol Tablets USP) tablets are indicated...

The Indications and usage section has been revised accordingly.

iv. DOSAGE AND ADMINISTRATION

Schedule #2, Day 1 start - The instructions do not allow for a day 1 start for the 28 day regimen. Please comment and/or revise.

The blister configuration (race track) was designed identical to the branded products, Norinyl 1+35, 1+50, and Brevicon and is deemed appropriate for day 1 starters. In addition, the instructions provided facilitate correct tablet taking such as: "take according to physicians instructions", "start in this row on day indicated", "follow the arrows", "take all white "active" tablets first".

v. *REFERENCES*

See GENERAL COMMENT i. Under INSERT.

The physician insert has been revised as requested.

c. *DETAILED PATIENT PACKAGE INSERT*

See GENERAL COMMENTS i and ii under INSERT.

The detailed patient package insert has been revised as requested.

d. BRIEF PATIENT PACKAGE INSERT

See GENERAL COMMENTS i and ii under INSERT.

The Brief Patient Package has been revised as requested.

Four copies of draft labeling is provided in attachment 20.

A side by side annotated comparison of Low - Ogestrel to Norinyl 1+35, including blister and carton comparison has been included in attachment 21.

If you have any questions regarding this submission, please contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (fax)

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SEARLE

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FAX (847) 982-4701

September 3, 1998

ORIG AMENDMENT

N/A B

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

Via Fax: (301)594-0181

RE: ANDA 75-288
Low-Ogestrel 21 and 28 day tablets
(norgestrel and ethinyl estradiol tablets USP, 0.3mg/0.03mg)
BIOEQUIVALENCY AMENDMENT
TELEPHONE REQUEST

Dear Mr. Sporn:

In accordance with 21 CFR 314.96 and in response to a telephone request from Lizzie Sanchez, SCS Pharmaceuticals hereby amends the above mentioned application with the potency results for the reference product used in the bioequivalence study.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (fax)

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May 18, 1998

Mr. Douglas Sporn
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AB

RE: ANDA 75-288
Low-Ogestrel
(norgestrel .3mg and ethinyl estradiol 0.03mg)
BIOEQUIVALENCY AMENDMENT

Dear Mr. Sporn:

In accordance with 21 CFR 314.96, and in response your fax (enclosed) dated May 1, 1998 SCS Pharmaceuticals hereby submits a Bioequivelancy Amendment to the above mentioned ANDA. Your comments, in italics, followed by our response are provided below:

1. *Please provide report of analytical study conducted for the assay of EE and NG in the study samples, including site, date, name(s) of investigator(s), analytical procedure, method validation, re-assay report, and chromatograms or raw data for at least % of the subjects randomly selected.*

The analytical study reports for assay of EE and NG are provided in the following reports: Validation of a High Resolution Gas Chromatography Method for the Determination of Ethinyl Estradiol in Human Plasma (EDTA) Using Negative Chemical Ionization Mass Spectrometry (Project No. 55023/DPV); Validation of a High Resolution Gas Chromatographic Method for the Determination of Norgestrel (Racemic Mixture) in 0.5ML of Human Plasma Using Negative Chemical Ionization Mass Spectrometry: Range: Project No. 55087/DWB; and Norgestrel and Ethinyl Estradiol, Report for the Evaluation of Integrity During Human Plasma Collection and Long Term Stability Evaluation in Human Plasma. These reports include the site, investigator(s) names, ✓ analytical procedure and method validation. Copies of the reports are provided in attachments, 1, 2 and 3 respectively.

Chromatograms for % of the subjects randomly selected are provide in attachment 4. The chromatograms are sorted by run and include the reference, standards, QC data and the [illegible] re-assays.

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Samples were re-assayed only for analytical reasons and the results of these re-assays are reported in the QC reports: Quality Control Data for the Determination of Ethinyl Estradiol in Human Plasma by a High Resolution Gas Chromatography Method Using Negative Chemical Ionization Mass Spectrometry Detection , Searle Study N5L-96-02-001, at and Quality Control Data for the Determination of Norgestrel In Human Plasma by a High Resolution Gas Chromatography Method Using Negative Chemical Ionization Mass Spectrometry Detection, Searle Study N5L-96-02-001 at (attachments 5 and 6).

2. *The Clinical study was conducted over a period of 7 months (11/8/96 - 6/1/97). Please provide the exact date of study drug treatments for each subject*

The exact date of study drug treatments for each subject is provided in attachment 7.

3. *Please provide evidence of approval of the study by an IRB.*

Evidence of IRB approval is provided in attachment 8.

4. *Please provide the potencies of test and reference drugs, the lot size of the test drug, and the expiration date of the reference drug.*

The Certificate of Analysis (page 920-921 of the original ANDA) for the test batch Lot#002, packaged Lot #PT-142-96, clinical lot #10242 is provided in attachment 9. The potency of Low-Ogestrel was 97.2 norgestrel and 99.9% ethinyl estradiol. The lot size kg (approximately tablets) is also provided on the Certificate of Analysis and on the formulation page of the batch record (also provided in Attachment 9). The reference product, LoOvral Lot 9958097, was purchased from the market place and was not tested for potency. The expiration date on the LoOvral marketed package is May 1999.

5. *Please provide reason(s) for completing only one period of the study for each of the following subjects: Subjects # 10, 15, 17,20, 103 and 915.*

The reasons subject # 10, 15, 17, 20, 103 and 915 completed only one period of the study is provided on the table provided in attachment 7.

6. *Please provide any possible clinical significance of changes in clinical laboratory test results obtained from pre-and post study periods. Please provide discussion of any possible effect of these changes on the outcome of the study.*

The principle investigator reviewed the abnormal laboratory results and determined that they were not clinically significant. A listing of the laboratory values and Dr. Laurent's review is provided in attachment 10.

7. *Please provide the components and composition of the test product.*

The components and composition of the test product (pages 648 and 649 of original ANDA) are provided in attachment 11. Also, provided for reference is the comparative statement (page 12) of the original ANDA submission.

8. *Please conduct in vitro dissolution testing on the same lot of test and reference products used for the in vivo bioequivalence study.*

The *in vitro* dissolution data provided on pagers 149-151 of the original ANDA submission are the dissolution results from the test and reference product used in the *in vivo* bioequivelance study. Lot PT 142-96 is the packaging lot number for clinical lot 10242. Lot # 002 (K6002) designates the bulk tablet lot number used for releasing tablets to the packaging area. The packaging is assigned a distinct batch number and packaged product sent to the clinical pharmacy for use in clinical studies, is assigned a distinct clinical lot number (lot 10242).

Provided in attachment 12 are the clinical pharmacy records showing assignments of the clinical lot number 10242 to the packaged lot PT 142-96.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
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March 3, 1998

Douglas Sporn, MD
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NDC

See email to Shirley II
H Semple 6/18/98

RE: ANDA 75-288
Low-Ogestrel
(norgestrel and ethinyl estradiol Tablets 0.3/0.03 mg)
AMENDMENT - METHOD VALIDATION SAMPLES

Dear Dr. Sporn:

In response to the request from the Detroit District Laboratory, G. D. Searle hereby submits the following:

- 300 norgestrel and ethinyl estradiol tablets, 0.3 mg/0.03mg, from the bioequivalence lot 002. This lot is within its tentative 2 year expiration.
- Test methods.
- A copy of the worksheet for the analysis of lot 002 with calculations, results and associated spectra and chromatograms.

In addition reference standards are included with this request.

These materials have been forwarded as requested to the Detroit District Laboratory.

If you have any questions regarding this matter please contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (fax)

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cc: Ms. Shirley A. L. Ii, ANDA Team Leader
Detroit District Laboratory
1560 East Jefferson Ave.
Detroit, MI 48207

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75-288

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

NEW CORRESP

NC

December 24, 1997

noted NAI Silvia 2/17/98

Mr. Jeremiah Beckwith Jr.
Director of Investigations
FDA San Juan, District Office
Stop 8 ½ Fernadez Juncos Avenue
Puerta de tierra Station
San Juan, Puerto Rico 00906

Re: ANDA - Original Submission
Low-Ogestrel® 0.3/30-21 and 28
(0.3 mg and ethinyl estradiol 0.03 mg)

Dear Mr. Beckwith:

SCS Pharmaceuticals hereby submits a field copy of the above mention ANDA dated December 24, 1997.

SCS Pharmaceuticals certifies that this is a true copy of the application submitted to FDA headquarters in Rockville, Maryland.

If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (Fax)

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DF to Beckwith ANDA

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

Ok. to file S. Middleton
2-2-98

December 24, 1997

Douglas Sporn, MD
Office of Generic Drugs
Food and Drug Administration
Document Control Room 154
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

SEARLE

RE: ANDA Original Submission
Low-Ogestrel® 0.3/30 - 21 and 28 Tablets
(norgestrel 0.3mg and ethinyl estradiol 0.03 mg)

Dear Dr. Sporn:

SCS Pharmaceuticals submits herein the Abbreviated New Drug Application for Low-Ogestrel® 0.3/30-21 and 28 (norgestrel/ethinyl estradiol) Tablets, an oral contraceptive product. This application has been formatted according to the content and format guidelines in the Guidance For Industry: Organization of an Abbreviated New Drug Application, April 1997. A copy of the Chemistry, Manufacturing and Controls Section of the application has been sent to the San Juan, Puerto Rico District Office.

Please contact me with any question you may have.

Sincerely,

Doranne Frano

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(847) 982-7691
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