CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75803

CORRESPONDENCE

ANDA 75-803

Barr Laboratories, Inc.
Attention: Christine Mundkur MAR 27 2000
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

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: Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.1 mg/ 0.02 mg

DATE OF APPLICATION: February 15, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 17, 2000

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

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

Should you have questions concerning this application, contact:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

February 15, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Levia™ 21 and **Levia™** 28 day regimens.

In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. is submitting an Abbreviated New Drug Application for **Levia™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) – **Levia™** 21 and **Levia™** 28 day regimens.

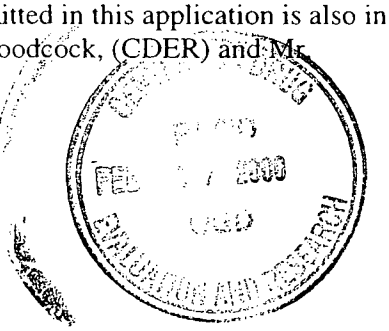
The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 11 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. The bioequivalence part of the review copy is contained in an orange binder consisting of 9 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and its outside contractors. Field Copies of this application have been forwarded to the New York and Chicago District Offices.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).



If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 15, 2002

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Rockville, Maryland 20855-2773

AMENDMENT
N/FA

TELEPHONE AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-803
Lessina™ 21 and Lessina™ 28 day regimens
(levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) Lessina™ 21 and Lessina™ 28 day regimens.

Reference is also made to the January 31, 2002 and February 13, 2002 teleconferences with Ruby Wu and Takiar Neeru of OGD and Christine Mundkur concerning the limit for total impurities. During the conference call, OGD officials and Barr agreed to tighten the total impurities/degradation products to % for the drug product based on the observed values for total impurities obtained from stability studies generated by Barr. Barr also agreed to maintain the specification for %.

As discussed during the teleconference, Barr is submitting the impurities/degradation products data obtained for a number of recently manufactured batches as well as a summary of the 24 months CRT stability for the original submission batch.

The data from recent batches and 24 months CRT stability of Lessina™ are provided in Table 1 and Table 2 respectively.

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The data shows values as high as % under accelerated conditions and as high as % at room temperature for batches up to 6 - 9 months old. Additionally, although was observed at % under 3 month accelerated conditions for batch 109651001T, Barr has real time stability data collected up to 24 months (Table 2) under CRT conditions that meets the current specifications of % for the submission batch (109659R01).

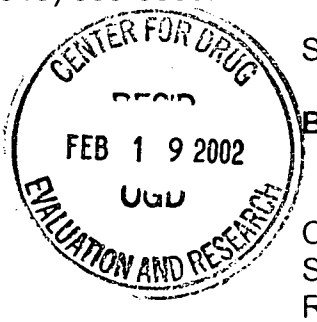
It is important to note that some analytical variability in the data is expected for ethinyl estradiol impurities/degradation products. Ethinyl Estradiol does not have a characteristic spectrum and the maximum absorption is around nm, which is the wavelength used for the impurities method. In addition, the low potency of ethinyl estradiol at mg/tablet contributes to the analytical variability associated with the impurities method.

Based on the data obtained with these batches, Barr is proposing new specifications for total impurities as follows:

Table 3: Proposed Specifications

The revised specification sheets and test methods are provided in the following pages.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.



Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 13, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/FA.

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Lessina™ 21 and Lessina™ 28 day regimens.
MINOR AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) Lessina™ 21 and Lessina™ 28 day regimens.

Reference is also made to the December 5, 2001 minor deficiency letter in which the following is stated:

A. Deficiencies:

Comment 1:

The acceptance limit for residual toluene for Ethinyl Estradiol durg substance is high. Please lower the limit.

Response:

Barr has already revised the acceptance limit for residual solvent toluene in ethinyl estradiol drug substance to NMT % to be consistent with the ICH recommendations. The updated raw material specification sheet and the test method are provided in Attachment 1.

Comment 2:

Please tighten the specification for and total impurities to be closer to the highest impurities level obtained in your telephone amendment dated November 12, 2001. Please revise and submit the final drug product release and stability specification.

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Response:

In response to the Agency's request, Barr reviewed the impurities and degradation products test results obtained from the stability studies conducted for Lessina™. Since Lessina™ and Portia™ (75-866) formulations and packaging configurations are very similar, the test results for Portia were also reviewed and the data for both products at 24 month are presented in Table 1 below. The data shows that the highest were observed at % and %. Please note that both of these impurities are degradation products of ethinyl estradiol. The total impurities and degradation products were found to be as high as %. In preparation for the launch of these products, Barr recently manufactured additional batches of each of these products. Barr reviewed the stability data of these recently manufactured batches of Lessina™ and Portia™ that indicate total impurities as high as % at 6 month CRT test station. The data are provided in Tables 2 and 3.

Table 1: Impurities and Degradation Products for Lessina and Portia Submission Batches

Table 2: Impurities and Degradation Products for a recent Lessina™ Batch 109651001T

Table 3: Impurities and Degradation Products for a recent Portia™ batch 109921001T

Based on the data obtained with these two ethinyl estradiol containing products, innovator products (provided in prior submissions) and the inherent variability of the impurities and degradation methods of low potency products, Barr is tightening the specifications for
impurities as follows:

Table 4: Proposed Specifications

The revised specification sheets and test method are provided in Attachment 2.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
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Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

DRUG AMENDMENT
N/Am

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-803
Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Lessina™ 21 and **Lessina™** 28 day regimens
TELEPHONE AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) Lessina™ 21 and Lessina™ 28 day regimens.

Reference is also made to a telephone conference held on October 31, 2001 between Barr Laboratories Inc., (Barr) and the Office of Gneric Drugs (OGD) concerning a number of Levonorgestrel and Ethinyl Estradiol products. Ms. Ruby Wu, Dr. David Gill, Dr. Andre Raw and Ms. Takiar Neeru of OGD and Christine Mundkur, Emad Alkhawam, Iltifat Hasan, Zhijun Jiang, Xiaotang Huang and Sharif Ahmed of Barr participated in the conference call. During the conference call, OGD officials raised concerns related to the increased levels of impurities and degradation products that have been reported in the August 22, 2001 telephone amendment for these ethinyl estradiol containing products.

OGD officials requested Barr to qualify the impurities and degradation products by comparing these with the impurities and degradation products observed in the innovator products. In addition, it was requested that an effort should be made to demonstrate a reasonable mass balance between the potency of the active ingredients and the impurities and degradation products.

As requested by the Agency, Barr attempted to obtain innovator products that are close to their expiration date. Although every attempt was made to source products close to their expiration date, lots ranging from already expired to recent production were procured. A number of batches of Levlite®, Nordette®, Allesse® and Triphasil® were tested for impurities and degradation products.

The impurities and degradation products test results for the above mentioned products are provided in Attachment 1. A comparison of the data from the innovator products and three of Barr's ethinyl estradiol containing products is provided in Table 1. The data demonstrates that
observed in the Barr and innovator products are at similar level.
is observed at a slightly higher level in Barr's products.
nknowns are observed at
higher levels in the innovator products. Overall, the total impurities and degradation products in the innovator products are slightly higher than Barr's products.

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Table 1: Impurities and Degradation Products for Barr and Brand Products

RRT= Relative Retention Time.
DBNQ= Detected But Not Quantitated.
N/D= Not detected.

Barr has calculated and presented in Table 1 the standard deviations and 3 times the standard deviations for the impurities observed in the innovator products. Based on the data obtained with Barr's ethinyl estradiol containing products, innovator products, drug substance manufacturer's specifications and the inherent variability of the impurities and degradation methods of low potency products, Barr is revising the specifications as follows:

Table 2: Proposed Specifications

Barr also reviewed the potency of Lessina™ (levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg) at the last test points and compared it with the total impurities and degradation products. With the change in the analytical method that permitted reporting of additional impurities and degradation products more impurities and degradation are observed. Please note that ethinyl estradiol does not have a characteristic spectrum and the maximum absorption is around nm, which is the wavelength used for the impurities method. In addition, Barr does not know all of the response factors of these impurities. Therefore, for the reasons mentioned and due to the low potency and the analytical variability associated with impurities methods, it was expected that a near mass balance between the assay and impurities can not been achieved.

Barr has made every effort to address the Agency concerns about the analytical methodology and stability of the Levonorgestrel and Ethinyl Estradiol Tablets, 0.1 mg/ 0.02 mg. This concludes the present amendment, which addressed the last remaining chemistry issues for this application.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

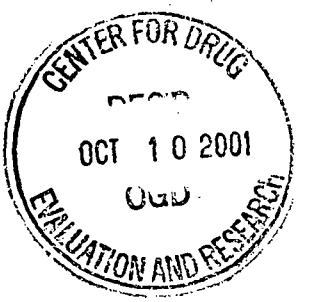
Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

ORIG AMENDMENT
N/AM

October 5, 2001



Office of Generic Drugs
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Metro Park North II
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REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Lessina™ 21 and **Lessina™** 28 day regimens
TELEPHONE AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lessina™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Lessina™** 21 and **Lessina™** 28 day regimens.

Reference is also made to a telephone conference held on August 22, 2001 between Barr Laboratories Inc., (Barr) and the Office of Generic Drugs (OGD) concerning a number of Levonorgestrel and Ethinyl Estradiol products. Ruby Yu, Paul Scwartz, Albert Mueller, David Gill and Ubrani Venkataram of OGD and Christine Mundkur, Iltifat Hasan and Sharif Ahmed of Barr participated in the conference call. During the conference call, OGD officials raised concerns related to the drop in the ethinyl estradiol potency and Barr's test method for impurities and degradation products for these ethinyl estradiol containing products.

Based on the Agency's concern regarding the current test method for the impurities and degradation products that was raised during the August 22 conference, Barr made an effort to detect and monitor two additional potential impurities, Barr also explored the prospect of changing the wavelength from nm and either reducing the limit of quantitation or reporting values below the LOQ of the analytical method. Based on the findings of this endeavor, Barr has revised the test method that permits reporting of additional impurities and degradation products. Following is a brief description of the studies that were performed in Analytical R&D to address the concerns regarding the impurities and degradation products of Ethinyl Estradiol (EE).

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Therefore, based on the Agency's suggestion, changing the wavelength to nm and quantitating all impurities above the limit of detection resulted in detection of and reporting of additional unknown impurities.
Thus, Barr has revised the test method for Levonorgestrel and Ethinyl Estradiol Tablets, 0.10 mg/ 0.02 mg to incorporate the following changes:

4. Based on the reprocessed data, the specification for impurities has been revised as follows:

NMT %
NMT %
NMT %
NMT %
NMT %
NMT %
NMT %
NMT %

The revised acceptance tests for in-process & finished product and quality control test specification sheets are provided.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

August 13, 2001

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DRUG AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Lessina™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Lessina™ 21 and **Lessina™** 28 day regimens.
TELEPHONE AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lessina™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Lessina™** 21 and **Lessina™** 28 day regimens.

Reference is also made to an August 2, 2001 phone conversation among Ruby Yu, Project Manager, Dr. David Grill, Team Leader, OGD, FDA and Christine Mundkur, Vice President of Quality and Regulatory Counsel, Barr Laboratories, Inc. regarding changes to packaging configurations for Lessina.

As stated in Barr's July 5, 2001 Labeling Amendment, Lessina will be packaged in blisters of 21 and 28 tablets. These blister's will then be placed within a fold over card. The dose cards will be packaged in aluminum pouches along with the days of the week stickers, combination detailed patient labeling and brief summary, and vinyl wallets. Six of the pouches will be packaged in a carton along with one package insert. Side by side comparison of the new packaging configuration and labeling components were also provided in the July 5, 2001 amendment.

Following Barr's July 5, 2001 Labeling Amendment, it was decided that a desiccant will be added to the pouch. This decision is based on Barr's experience with other levonorgestrel and ethinyl estradiol containing products that indicated that the desiccant may help improve the stability of such products by absorbing the moisture present within the pouch.

In accordance with the Guidance For Industry, Changes to an Approved NDA or ANDA, Section IX, C.2, Barr planned to file this change, post approval, in a supplement-Changes Being Effected. Since the agency requested additional clarification on the packaging configuration, we are providing the information concerning the addition of desiccant in this amendment.

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As such, a change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form products is considered annual reportable as long as in the new package provides the same or better protective properties (Guidance For Industry, Changes to an Approved NDA or ANDA, Section IX, D.5). Please note that even though the change involves the addition of a desiccant, it is only a secondary packaging component and does not come in contact with the product.

Furthermore, Barr looked into the possibility of printing ink leeching and permeating through the pouch and dose card into the blisters. As provided in this amendment, all printed matters are imprinted on the outer side of the secondary packaging component. Any leeching of ink is therefore not feasible, thus no further leeching study is necessary.

Based on the above information, Barr believes that the change will have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product. Therefore, Barr commits to place batches packaged with the desiccants in long-term stability and report the results in annual report.

Please note that, Barr has provided stability data in the original application and subsequent amendments for Lessina packaged in blisters only. As previously commented, the blister only configuration without any pouch or desiccant is a worst case scenario. The stability data indicated that the product is stable even in the worst packaging configuration.

The following information for Desiccant, 1 gram, 2 in 1 Packet (60/40 Mix), 07-0143 is provided in Attachment 1.

- DMF Authorization Letter (DMF
- Material Specification
- Barr's current QC Raw Material Specification & Test Record
- Barr's current QA Packaging Component Inspection Report
- Manufacture's Certificate of Analysis (Manufacturer's Lot 0000015090)

The following information concerning the pouch is provided in Attachment 2.

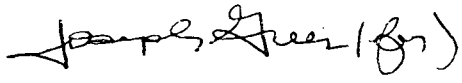
- DMF Authorization Letter (DMF
- Specification
- Pouch Diagrams
- Material Specification
- Certification of Compliance (Lot # 7-43614)

As requested, we are also providing samples of the complete package (six blister cards), as it will be marketed. Please note that the tablets were punched out of the blisters after blistering and before pouching for submission purposes.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 7, 2000

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Center for Drug Evaluation and Research
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Rockville, Maryland 20855-2773

ORIG AMENDMENT
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MAJOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Levia™ 21 and **Levia™** 28 day regimens.

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Levia™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Levia™** 21 and **Levia™** 28 day regimens.

Reference is also made to the July 31, 2000 major deficiency letter. The deficiencies identified in the comment letter and Barr's responses are as follows:

COMMENT 1:

Please include into the qualitative list of components for coating and provide the revised hard copy.

RESPONSE:

Barr inadvertently left out of the qualitative list of components. The hard copy of the revised qualitative list of components is attached as Attachment I.

COMMENT 2:

Please provide a cGMP certification statement for the 2150 Perrowville Road, Forest, VA 24551 Facilities.

RESPONSE:

The cGMP certification provided in the original application, page 09-00024, is a blanket statement for all of Barr's facilities, including the Virginia facility located at 2150 Perrowville Road, Forest, VA 24551. To assure the Center of the cGMP standards at all of Barr's facilities, a revised cGMP certification is provided as Attachment II that specifically lists the facilities involved in the manufacture, packaging and processing of all of Barr's products.

COMMENT 3:

Please note that the DMF , Levonorgestrel, is currently inadequate. The DMF holder, has been notified.

RESPONSE:

We acknowledge the Agency comment concerning DMF

COMMENT 4:

Please either include testing of organic volatile impurities to the drug substance release specifications or provide a letter from both drug substance manufacturers stating that none of the listed solvents in the USP 24 <467> are used in the manufacturing processes of the drug substance Levonorgestrel USP and Ethinyl Estradiol USP.

RESPONSE:

The drug substance manufacturers, , have certified that none of the listed solvents in the USP 24 <467> are used in the manufacturing processes of Levonorgestrel, USP and Ethinyl Estradiol, USP respectively. The OVI statements are provided as Attachment III.

COMMENT 5:

Please provide the specification and test result for % particle size for both drug substances, Levonorgestrel USP and Ethinyl Estradiol ESP and retest them annually.

RESPONSE:

The QC Raw Material Specifications and Test Records were updated to include %, specifications for both of the drug substances.

Barr reevaluates raw materials annually for the parameters that have the potential to change over time. Since particle size of levonorgestrel and ethinyl estradiol are not expected to change over time Barr believes that it not necessary to retest them. The revised Specifications and Test Records are provided in Attachment IV.

COMMENT 6:

Specification for known impurity i.e. in Levonorgestrel USP is high. Please reduce it based on the observed values.

RESPONSE:

Barr has observed levels ranging from %. The drug substance manufacturer for Levonorgestrel USP specifies an impurity limit of NMT %. In view of this, Barr has conducted a computational toxicity assessment of The study, conducted by the for Barr, concluded that if present at % in levonorgestrel (equivalent to 15 mcg per day) would be safe. Based on the observed values and this report, Barr will maintain the specification for %. A summary of the assessment is provided in Attachment V.

COMMENT 7:

Please provide assurance that will use the correct Packaging and labeling documentation for future batches of the subject drug product (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg).

RESPONSE:

The master that was used for the packaging of Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg has been superseded since the submission batch was blistered. The revised master contains the correct product name, Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg. Please note that creation or revision of a packaging master is reviewed and approved by designated quality assurance and regulatory affairs personnel at . and Barr. The packaging master for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg identifies specific components with appropriate revisions and provides detailed procedures for packaging and control.

COMMENT 8:

Please provide one time test data to demonstrate the integrity of the sealed blister pack (e.g. leak test).

RESPONSE:

. tests blister packs every 60 minutes during packaging of every job for seal integrity. This test requires that the blister pack The test requirements are contained in the Quality Control Specifications and were provided in the Original Application on pages 12-00094 and 12-00122 for Levia™ 21 and Levia™ 28 respectively. The test results for the submission batch were recorded as "AC" for acceptable in the QC In-Process sheets on pages 12-00104 and 12-00133 for Levia™ 21 and Levia™ 28 respectively. Copies of these QC In-Process sheets are provided in Attachment VI.

COMMENT 9:

Please provide the Quality Control Inspection Requirements for the packaging material used in the test batches.

RESPONSE:

The quality control inspection requirements for the packaging material used in the test batches were provided as Material Specifications in the original application, pages 12-00087 and 12-00113 for the film (base) and pages 12-00089 and 12-00115 for the foil (lidding). Upon receipt of these materials, quality control inspects and records their findings on Receiving Inspection sheets, and then releases or rejects the materials. Copies of Material Specifications and Receiving Inspection sheets for the film and foil are provided in Attachment VII.

COMMENT 10:

Please provide the bulk container/closure information including the testing used for shipping the drug product to the contract packager.

RESPONSE:

The bulk container/closure used for levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg consists of the following:

1. Polyethylene bags, doubled
2. Double walled corrugated carton

Please note that the bulk container/closure information was provided as part of the executed manufacturing master in the original application. On page 12-00020, Step 31 describes the bulk container/closure system as "clean, tared, properly labeled, double polyethylene lined containers".

In order to ensure that the finished product stored and shipped in bulk maintains its integrity and stability, Barr conducted stability studies with the above mentioned double polyethylene bags (i.e. the primary container). Please note that the double polyethylene bags without the double walled corrugated carton represents a worse case. The stability information of the finished product in bulk was provided on pages 16-00024A - 16-00024E of the original application.

COMMENT 11:

Please provide a method (including a sampling plan) and commitment for performing the in every production batch, since the current test only applies to the validation batches according to the process validation protocols. In addition, please also note that the RSD of assay should be reduced to NMT %.

RESPONSE:

testing is performed in accordance with Barr's test method and Barr's Standard Operating Procedures for Bulk Blend Sampling and Blend Content Uniformity Testing and Retesting.

Barr's testing is similar to USP <905> in that it is a stage testing. Stage 1 consists of three samples representing the beginning, middle and end of the batch. Stage 1 specifications require that all three samples must be within the finished product assay specification. Should one or more of Stage 1 results not meet Stage 1 specifications, Stage 2 testing is conducted. Stage 2 testing consists of retesting all three of the original locations, including the location that did not meet stage 1 requirements [total samples for retesting is 7 to 9]. All individual results for Stage 1 and 2 must be within 85.0 – 115.0% as specified in the USP <905>, the average for Stage 1 and Stage 2 testing must be within the finished product assay limit, and the RSD must be within 6.0%.

Barr does not agree with the Agency's recommendation to revise the RSD to %. is still a draft guidance. The industry was recently informed that this draft guidance is again being revised and will be reissued as a draft. Additionally, this guidance will remain in draft until such time that has studied the issue and proposed recommendations. It is important to note that Barr has committed to conducting testing as a routine in-process test for this product. Until FDA has finalized the guidance, Barr intends to continue using the specifications that were agreed upon between Barr and FDA as a result of the 1993 court decision.

Barr's Standard Operating Procedures, containing the specifications, sample size and procedures for testing and retesting, have been reviewed and approved by the New York and New Jersey District Offices, Office of Compliance and the U.S. Attorneys Office in accordance with the "Barr Decision" and subsequent Court Order. Based on these prior agreements between Barr and FDA concerning testing, Barr will not adopt the agency's proposal outlined in the above recommendations. Barr will continue to adhere to our established standard operating procedures for the number of samples, sample size, specifications, and testing and retesting procedures for Barr is currently corresponding with the Office of Generic Drugs, in particular, Dr. Dave Gill, Team Leader concerning the RSD Specification for all of Barr's applications containing

COMMENT 12:

Please provide the target specification for weight, thickness, and hardness in the in-process controls for levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 and placebo tablets.

RESPONSE:

The target specifications for weight, thickness, and hardness are indicated on the manufacturing masters in addition to the range for the in-process controls. The tables for the in-process guidelines and specifications have been updated to include the targets for levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg and placebo tablets and provided in Attachment VIII.

COMMENT 13:

Please revise the impurities specification for drug product release and stability to label as individual known, individual unknown, and total. Each known impurity should be identified by its chemical name and specifications should be established based on the actual observed values. Please provide the test data accordingly on the certificate of analysis.

RESPONSE:

In view of this Agency comment, Barr has conducted additional studies for the impurities/degradation products test method. Based on the information provided by the drug substance manufacturers and the recent studies done with an improved method, we believe that the following potential impurities/degradation products may be present in the drug product.

Barr has reviewed the stability data generated for other levonorgestrel and ethinyl estradiol products to establish specification of these impurities. Barr has also tested Levlite™ and observed these impurities at or above the levels observed with Barr's drug product. The following table shows the impurities seen in Levlite™ and Barr's levonorgestrel and ethinyl estradiol tablets.

RESPONSE: (continued)

The drug substance manufacturers specify individual impurities of NMT %. The USP chromatographic purity for levonorgestrel also specifies a limit of NMT % for individual impurities. Based on the drug substance manufacturers' maximum allowable limit for these impurities, and the potential for these impurities to grow over time, Barr has tightened the specification for impurities/degradation products as follows:

Impurities	Release Specification	Stability Specification
	NMT %	NMT %
	NMT %	NMT %
	NMT %	NMT %
	NMT %	NMT %
	NMT %	NMT %
	NMT %	NMT %

The updated method has been validated and the method validation report RD 00-241 is provided in Attachment IX. The QC Specification and Test Record for release and stability and the marketed product stability protocol have been updated to reflect the known impurities, individual unknown, and total impurities. The updated Specifications and Test Method are also provided.

COMMENT 14:

Description acceptance criteria for finished product and placebo tablets in the electronic data show the tablets are debossed with "B". However, the tablets in the hardcopy are debossed with "b". Please clarify.

RESPONSE:

Barr has reviewed the data in EVA and ESD and confirmed that it states "b". Barr regrets if this error occurred during the transfer of data to FDA's database. The correct description of levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 is "pink, round, film-coated, biconvex unscored tablet. Debossed with 965 on one side and b on the other side".

COMMENT 15:

Please include a test and specification for the cross contamination of Levonorgestrel and Ethinyl Estradiol to your testing protocol for placebo tablets.

RESPONSE:

The test method describes the chromatographic procedure for identification of the placebo tablets. The identification of the placebo tablet requires absence of active ingredient peaks of levonorgestrel and ethinyl estradiol. Page 14-00017 of the original application contains the data

RESPONSE: (continued)

for the identification test. The test methods for the placebo tablets used in this submission are also contained in the original application, pages 15-00126 - 15-00131.

Please note that the placebo tablets are white in contrast to the active pink tablets. In addition, the Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg and placebo tablets are manufactured with different manufacturing masters and in different buildings that further reduces the potential for cross contamination.

COMMENT 16:

Please include the USP test and specification for disintegration for release and hardness for stability protocols for the placebo tablets.

RESPONSE:

Barr conducts in-process testing for friability and hardness throughout the manufacturing process. The results of the in-process testing are documented in the batch record. Friability and hardness are monitored during manufacturing in order to be able to adjust processing parameters to ensure the quality attributes of the finished product.

In this regard, we would like to draw your attention to the November 25, 1997 ICH Draft Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances. Section 3.3.2.1 (b) of the guidance states that "It is normally appropriate to perform hardness and/or friability testing as an in-process control (see section 2.3). Under these circumstances, it is not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification."

Since a placebo tablet is not an active tablet, disintegration and hardness do not have a critical impact on product quality. There has been no observable change in the product throughout the stability test intervals for the 12 months tested to date, see Attachment X. The stability samples of placebo tablets are tested for description. The tablets are pushed out of the blisters and the analyst's observation is recorded. This also ensures that the tablets can withstand considerable force, which is an indication of its hardness throughout the shelf life. Therefore, inclusion of these tests for stability purposes is not necessary.

COMMENT 17:

Please remove all the information pertaining to code number 0436 from the drug product and code number 0413 and 0231 from the placebo tablets acceptance tests and limits which are not the subject of this application, page 15-00088 and 15-00126 respectively.

RESPONSE:

The test method is used for levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg (product code 0965) and levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg (product code 0436). The test method is used for white biconvex placebo tablets (product codes 0208, 0143 and 0231). Please note that although the test methods include different product codes, it is the QC Specification and Test Record that is used to control and record the testing of specific products. QC Specification and Test Records are product specific documents. Further, Barr is not seeking approval for code number 0436, nor 0143 or 0231 in this application. Separate applications will be filed for the approval of these products.

COMMENT 18:

Please include the stability studies for 21-count blisters in your post approval stability protocol.

RESPONSE:

Barr Laboratories, Inc. has packaged levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg in blister cards of 21 day and 28 day regimens. The 21 day and 28 day regimens have been packaged in exactly the same blister container closure systems. For stability studies, Barr packaged levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg in blisters of 28 tablets. The blister package system consists of identical container closure with regards to material and size. Every blister has the exact same protection, compatibility and storage properties (surface area, moisture permeation, etc.) Therefore, each blister in a blister card is identical to all others regardless of whether the blister card contains 21 or 28 blisters.

There is no scientific or technical reason to conduct separate stability studies with various numbers of the same unit dose container closure. The FDA Guidance for Industry "Container Closure Systems for Packaging Human Drugs and Biologics" defines a *container closure system* as "the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system." According to the same guidance, the information that should be submitted in support of an original application for any drug product should include a general description of the entire container closure system. In addition, under Stability Data (Packaging Concerns), the guidance states that "Stability testing of the drug product should be conducted using the container closure systems proposed in the application. The packaging system used in each stability study should be clearly identified." Again, the FDA identifies *packaging system* as equivalent to a container closure system.

RESPONSE: (continued)

Even the FDA categorized "A change in container closure system of unit dose packaging (e.g. blister packs) for nonsterile solid dosage form products...." as a minor change in its Guidance for Industry: Changes to an Approved NDA and ANDA. The difference between a 21 day and 28 day blisters is not even a change in "container closure system". This is contrary to Agency's objective to streamline approval process and reduce needless testing. Therefore, Barr strongly believes that its stability program is based on scientific reasoning that provides sufficient stability data representative of both 21 day and 28 day package systems.

B.

COMMENT 1:

A satisfactory compliance evaluation of all of the facilities for drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

RESPONSE:

Acknowledged.

COMMENT 2:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

RESPONSE:

Acknowledged.

COMMENT 3:

Please provide all accumulated room temperature stability to date.

RESPONSE:

All of the room temperature stability data collected to date for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg is provided in Attachment X.

BIOEQUIVALENCY COMMENTS

COMMENT 1:

The Division of Bioequivalence has completed its review and has no further questions at this time.

RESPONSE:

Acknowledged.

COMMENT 2:

We acknowledge that the dissolution testing will be incorporated into your stability and quality control programs as specified in USP 24.

RESPONSE:

Acknowledged.

Identical copies of this Amendment have been provided to the New York and Chicago District Offices. A Document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 14, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AA

GRATUITOUS AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Levia™ 21 and **Levia™** 28 day regimens.

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Levia™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Levia™** 21 and **Levia™** 28 day regimens.

Barr Laboratories, Inc. inadvertently omitted the equivalency study in the method validation report for dissolution test procedure in our Abbreviated New Drug Application submitted on February 15, 2000. At this time, we are providing the Equivalency Study Report RD00-144 showing equivalency between USP and Barr's for dissolution test. Please note that all other method validation reports were provided in Section XV of the Original Application.

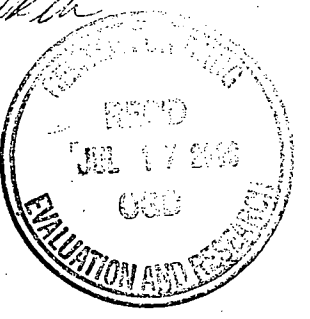
Identical copies of this Amendment have been provided to the New York and Chicago District Offices. A Document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel



Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 10, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N /AB

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Levia™ 21 and **Levia™** 28 day regimens.

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Levia™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Levia™** 21 and **Levia™** 28 day regimens.

We are providing Master Formula pages containing Batch Formulation and In-Process Controls for the Bioavailability/ Bioequivalence section for the following:

1. Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg
2. Intermediate Blend for White, Placebo tablets for Oral Contraceptives
3. White, Biconvex, Placebo Tablets for Oral Contraceptives

Please note that, the batch formulation and in-process controls were provided only in Section XI and XII of the Original Application.

Identical copies of this Amendment have been provided to the New York and Chicago District Offices. A Document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

CENTER FOR DRUG
REC'D
APR 11 2000
OGD
EVALUATION AND RESEARCH

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 14, 2000

NEW CORRESP

75-803 NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: **AMENDMENT TO PENDING ANDA**
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/ 0.02mg)
Levia™ 21 and **Levia**™ 28 day regimens.
Electronic Submission of CMC and BA/BE

Reference is made to our Abbreviated New Drug Application submitted February 15, 2000 under 505(j) of the Food, Drug and Cosmetic Act for **Levia**™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02mg).

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC and BA/BE electronic submission. The CMC and BA/BE electronic submissions are contained on separate diskettes labeled " CMC ESD & Companion Document" and BA/BE ESD" respectively. Backup diskettes containing identical information for both the CMC section and the BA/BE section are also provided.

The CMC ESD file is named "BRL0001.003" and the Microsoft Word Companion Document file is named "BRL0001.004". The BA/BE ESD is named "BRL0001.001" and the Microsoft Word Companion Document file is named "BRL0001.002".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the New York and Chicago District Offices.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 11, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NC

NEW CORRESP

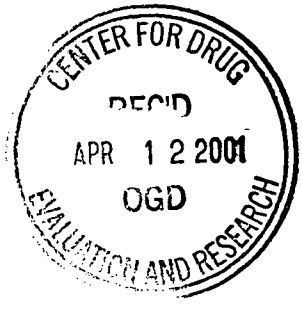
REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Gestryn™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Gestryn™ 21 and **Gestryn™** 28 day regimens.
TELEPHONE AMENDMENT

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Gestryn™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Gestryn™** 21 and **Gestryn™** 28 day regimens.

Reference is also made to an April 11, 2001 phone conversation between Ruby Yu, Project Manager, OGD FDA and Sharif Ahmed, Manager of Regulatory Affairs, Barr Laboratories, Inc. regarding the test method for Ethinyl Estradiol, USP. Ms Yu requested Barr to revise the test method and specification for Ethinyl Estradiol to conform to USP 24, Supplement 3.

In accordance with USP 24 Supplement 3, Barr had already revised the test method and specification for Ethinyl Estradiol, USP. Updated QC Raw Material Test Specifications & Test Record and Acceptance Test for Raw Materials are provided.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.



If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 2, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

VIA ONG AMENDMENT AC

AMENDMENT TO PENDING APPLICATION

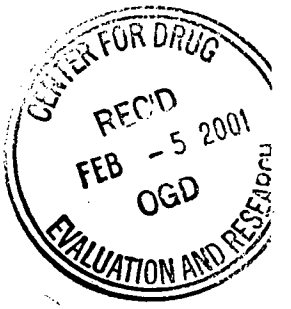
REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-803
Gestryn™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Gestryn™ 21 and **Gestryn™** 28 day regimens.

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Gestryn™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Gestryn™** 21 and **Gestryn™** 28 day regimens.

Reference is also made to a February 1, 2001 phone conversation between Ruby Yu, Project Manager, OGD, FDA and Elisabeth Noble Gray, Barr Laboratories, Inc. regarding the filing of a change in the manufacturing site of the active pharmaceutical ingredient ethinyl estradiol (supplied by). In accordance with Ms. Yu's instructions, we are filing this change as an Amendment to the pending application.

The manufacturing sites are as follows:

Current Site:



Alternate Site:

site was inspected and approved by FDA in 1998. In July 1999, FDA set forth requirements for both and their customers for the transfer of products to the new facility. fulfilled all requirements and submitted an amendment to the relevant DMF's (see updated authorization letter to reference DMF which includes the

In accordance with FDA's July 20, 2000 communication to (see attached), Barr hereby commits to place the first commercial batch of levonorgestrel and ethinyl estradiol tablets, USP using the new source of drug (new site) on stability under Barr's proposed stability protocol to support Barr's approved packaging configurations.

Please note that the processes at the site do not differ materially from those of the site. Also, a GMP inspection covering the processes that are representative of process used for the four new drug substances was performed in October 2000. A 483 was issued and contained minor comments. believes they provided more than adequate responses in their November 2000 correspondence that satisfied FDA's concerns. There have been no further communications regarding this 483 issued to by FDA. Please note that FDA does not issue an acknowledgment or "approval" letter upon receipt of a satisfactory manufacturer response. It is normal practice for FDA to only respond to the manufacturer if the response is inadequate.

Enclosed please find the following documentation:

- Copy of authorization letter (dated 8/21/00) to reference their DMF No for Ethinyl Estradiol as last updated on 1/3/2000. Please note that is owned by the parent company Therefore, the enclosed DMF letter is on letterhead.

- Copy of the July 20, 1999 From FDA to regarding the filing requirements.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

C. Barnes for

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NEW CORRESP
NC

March 9, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

GENERAL CORRESPONDENCE [redacted]

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
Levia™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg)
Levia™ 21 and **Levia™** 28 day regimens.

Reference is made to our Abbreviated New Drug Application submitted on February 15, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Levia™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) **Levia™** 21 and **Levia™** 28 day regimens.

Please be advised that at this time we are submitting additional information regarding DMF authorization for the bulk drug substances levonorgestrel and ethinyl estradiol. In accordance with the April 8, 1994 Letter to Industry regarding the letter of authorization from the DMF holder, we are herewith submitting the following additional documents:

- A revised Letter of Authorization from the US Agent for DMF authorizing Barr Laboratories, Inc. to reference the above mentioned DMF for levonorgestrel.
- Statement from the DMF holder, permitting to represent in all matters pertaining to DMF
- Letter of Authorization from US Agent for DMF authorizing Barr Laboratories, Inc. to reference the above mentioned DMF for ethinyl estradiol. This has been provided in the original application.
- Satement from the DMF holder, permitting to represent in all matters pertaining to DMF

Please be advised that identical copies of this Correspondence have been provided to the Baltimore District Office. A Document certification is attached.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 10 2000
OGD