CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75803

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA:	CHEMIST:	DATE:
75-803	Neeru B. Takiar	February 27, 2002

DRUG PRODUCT:

Levonogestrel and Ethinyl Estradiol Tablets, USP

FIRM:

Barr Laboratories, Inc.

DOSAGE FORM:	STRENGTHs:
Tablets	0.1 mg/0.02 mg (21 and 28 Days regimens)

cGMP:

EER acceptable on April 17, 2001.

BIO:

Bio acceptable by J Chany on 5/23/00; signed off on 5/25/00.

VALIDATION - *(Description of dosage form same as firm's):*

The DS and DP are covered by monograph in the USP 24. Method Validation is not required.

STABILITY:

The firm has provided satisfactory 3 months accelerated and up to 18 months room temperature stability data for blister packaging (0.1 mg/0.02 mg and placebo tablets) and 12 months room temperature stability data for the bulk product (0.1 mg/0.02 mg and placebo tablets). The stability data support an expiration period of 18 months.

LABELING:

Labeling is acceptable on July 12, 2001.

STERILIZATION VALIDATION *(If applicable)*:

N/A

SIZE OF BIO BATCH *(Firm's source of NDS ok?)*:

Size of the bio batch for 0.1 mg/0.02 mg (Active) is tablets. The drug substances, Levonogestrel is manufactured by and was found adequate on 3/30/01 and Ethinyl Estradiol is manufactured by and was found Adequate on 7/27/00.

SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?):*

Size of stability batch is same as that of the bio batch.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

Size of the proposed production batch for 0.1 mg/0.02 mg (Active) tablets is same as that for the bio batch.The manufacturing process is identical to the exhibit batch.

Signature of chemist:	Signature of supervisor:
/S/ 2/28/02	/S/ 3-4-02
Neeru B. Takiar/ 2-27-02	Dave Gill, Ph.D.

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OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   1

2. ANDA NUMBER
   75-803

3. NAME AND ADDRESS OF APPLICANT
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. LEGAL BASIS for ANDA SUBMISSION
   The listed reference drug product is **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg Tablet; Oral-21 Day Regimen – NDA 20860) manufactured by Berlex Laboratories.

   On July 13, 1999, the Agency approved a citizen petition, Docket No 99P-0189/CP1, filed by McKenna & Cuneo, L.L.P. for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg to designate **Levlite™** 21 tablets manufactured by Berlex Laboratories as an alternate reference listed drug (Section II, page 02-00007). Barr's Abbreviated New Drug Application for **Levia™** 21 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) and **Levia™** 28 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) are based on **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) tablets 21 day regimen.

   The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens and are not entitled to a period of marketing exclusivity. (Section III page 03-00001 and 2)

5. SUPPLEMENT(s)
   None

6. NAME OF DRUG
   LEVIA

7. NONPROPRIETARY NAME
   Levonorgestrel and Ethinyl Estradiol Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR
   None

9. AMENDMENTS AND OTHER DATES
   02-15-2000 Original submission
   03-09-2000 New Correspondence
   03-27-2000 Letter of acceptance

10. PHARMACOLOGICAL CATEGORY
    Oral Contraceptive

11. HOW DISPENSED
Prescription

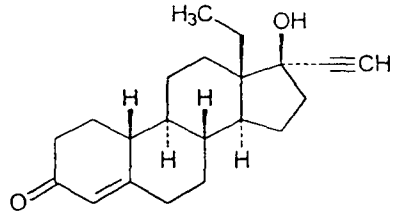
12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Levonorgestrel USP (micronized)			v1.2, p08-00004
Ethinyl Estradiol USP (micronized)			v1.2, p08-00052
Film			v1.3, p13-00016
Push Thru Foil 0.001			v1.3, p13-00018

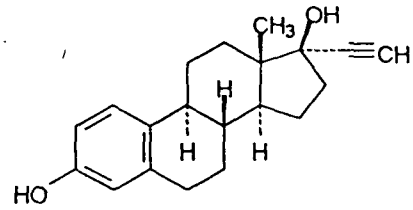
13. DOSAGE FORM
Tablet

14. POTENCY
0.1 mg/0.02 mg (21 and 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Levonorgestrel. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17□)-, (-)-.$C_{21}H_{28}O_2$. 312.45. 797-63-7. Progestin. USP 24, page 965.



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are not satisfactory:
- 20. Components and Composition
- 21. Facilities and Personnel
- 22. Synthesis
- 23. Raw Material Controls
- 25. Manufacturing and Processing
- 26. Container
- 28. Laboratory Controls (In-Process and Finished Dosage Form)
- 29. Stability

The following sections are pending:
- 32. Labeling
- 33. Establishment Inspection

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Chem Review #1

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   2

2. **ANDA NUMBER**
   75-803

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Levlite**™ (levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg Tablet; Oral-21 Day Regimen – NDA 20860) manufactured by Berlex Laboratories.

   On July 13, 1999, the Agency approved a citizen petition, Docket No 99P-0189/CP1, filed by McKenna & Cuneo, L.L.P. for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg to designate **Levlite**™ 21 tablets manufactured by Berlex Laboratories as an alternate reference listed drug (Section II, page 02-00007). Barr's Abbreviated New Drug Application for **Levia**™ 21 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) and **Levia**™ 28 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) are based on **Levlite**™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) tablets 21 day regimen.

   The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim **Levlite**™ (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens and are not entitled to a period of marketing exclusivity. (Section III page 03-00001 and 2)

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   LEVIA

7. **NONPROPRIETARY NAME**
   Levonorgestrel and Ethinyl Estradiol Tablets, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**

02-15-2000	Original submission
09-07-2000	Major Amendment-Response to deficiency letter of 7/31/2000
10-04-2000	Electronic submission of CMC Amendment
02-02-2001	Amendment to pending application - BU specifications and alternate manufacturing Site for active ingredient, Ethinyl Estradiol.

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

11. HOW DISPENSED
Prescription

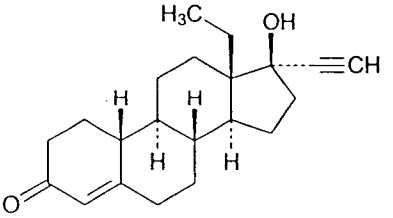
12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Levonorgestrel USP (micronized)			v1.2, p08-00004
Ethinyl Estradiol USP (micronized)			v1.2, p08-00052
Film			v1.3, p13-00016
Push Thru Foil 0.001 (hard)			v1.3, p13-00018

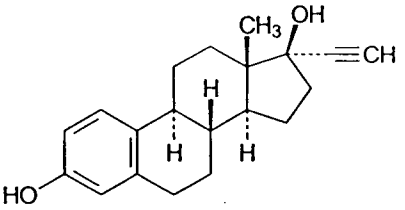
13. DOSAGE FORM
Tablet

14. POTENCY
0.1 mg/0.02 mg (21 and 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Levonorgestrel. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17□)-, (-)-.$C_{21}H_{28}O_2$. 312.45. 797-63-7. Progestin. USP 24, page 965.



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are *not* satisfactory:

22. Synthesis
28. Finished product
29. Stability

The following sections are pending:

32. Labeling

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable - MINOR.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/February 08, 2001

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Chem. Review #2

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   3

2. **ANDA NUMBER**
   75-803

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg Tablet; Oral-21 Day Regimen – NDA 20860) manufactured by Berlex Laboratories.

   On July 13, 1999, the Agency approved a citizen petition, Docket No 99P-0189/CP1, filed by McKenna & Cuneo, L.L.P. for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg to designate **Levlite™** 21 tablets manufactured by Berlex Laboratories as an alternate reference listed drug (Section II, page 02-00007). Barr's Abbreviated New Drug Application for **Levia™** 21 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) and **Levia™** 28 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) are based on **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) tablets 21 day regimen.

   The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens and are not entitled to a period of marketing exclusivity. (Section III page 03-00001 and 2)

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   LEVIA **(The proposed name "LESSINA™" was found acceptable by OPDRA on June 8, 2001)**

7. **NONPROPRIETARY NAME**
   Levonorgestrel and Ethinyl Estradiol Tablets, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**

02-15-2000	Original submission
03-09-2001	Minor Amendment-Response to deficiency letter of 02/16/2001
04-12-2001	Fax Amendment-Response to T-con dated 04/11/2001
07-06-2001	Labeling Amendment - reflect packaging configuration changes for Lessina
08-13-2001	Telephone Amendment - Response to T-con dated 08/02/2001
10-05-2001	Telephone Amendment - Response to T-con dated 08/22/2001
11-12-2001	Telephone Amendment - Response to T-con dated 08/31/2001

10. PHARMACOLOGICAL CATEGORY
Oral Contraceptive

11. HOW DISPENSED
Prescription

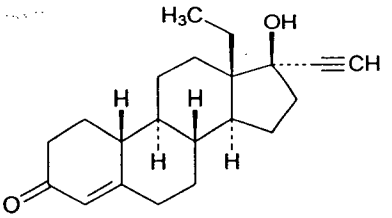
12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Levonorgestrel USP (micronized)			v1.2, p08-00004
Ethinyl Estradiol USP (micronized)			v1.2, p08-00052
Film			v1.3, p13-00016
Push Thru Foil 0.001			v1.3, p13-00018

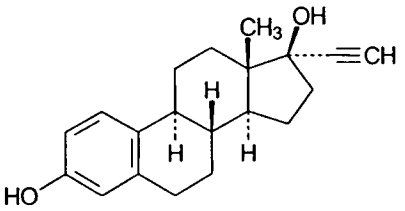
13. DOSAGE FORM
Tablet

14. POTENCY
0.1 mg/0.02 mg (21 and 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Levonorgestrel. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17□)-, (-)-.$C_{21}H_{28}O_2$. 312.45. 797-63-7. Progestin. USP 24, page 965.



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
None

18. CONCLUSIONS AND RECOMMENDATIONS
The application is **NOT Approvable - Facsimile**

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/November 23, 2001; November 30, 2001

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Chem. Review #3

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
4

2. **ANDA NUMBER**
75-803

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP, 0.1 mg/0.02 mg Tablet; Oral-21 Day Regimen – NDA 20860) manufactured by Berlex Laboratories.

On July 13, 1999, the Agency approved a citizen petition, Docket No 99P-0189/CP1, filed by McKenna & Cuneo, L.L.P. for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg to designate **Levlite™** 21 tablets manufactured by Berlex Laboratories as an alternate reference listed drug (Section II, page 02-00007). Barr's Abbreviated New Drug Application for **Levia™** 21 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) and **Levia™** 28 tablets (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) are based on **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) tablets 21 day regimen.

The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim **Levlite™** (levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg) 21 and 28 day regimens and are not entitled to a period of marketing exclusivity. (Section III page 03-00001 and 2)

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
LESSINA

7. **NONPROPRIETARY NAME**
Levonorgestrel and Ethinyl Estradiol Tablets, USP

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

02-15-2000	Original submission
12-13-2001	MINOR Amendment - Response to deficiency letter dated 12/05/2001
01-18-2002	T-CON, Confirmation of Expiration Date
02-15-2002	Telephone Amendment

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. HOW DISPENSED
Prescription

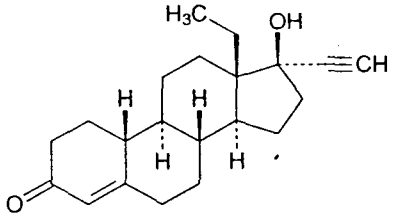
12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
Levonorgestrel USP (micronized)			v1.2, p08-00004
Ethinyl Estradiol USP (micronized)			v1.2, p08-00052
Aclar PA 160/02 Film			v1.3, p13-00016
Push Thru Foil 0.001 Al w/4506 (hard)			v1.3, p13-00018

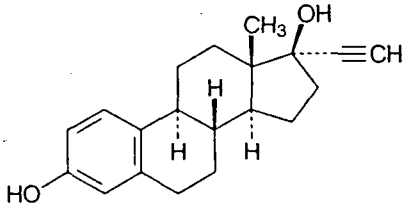
13. DOSAGE FORM
Tablet

14. POTENCY
0.1 mg/0.02 mg (21 and 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Levonorgestrel. 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17□)-, (-)-. $C_{21}H_{28}O_2$. 312.45. 797-63-7. Progestin. USP 24, page 965.



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
None

18. CONCLUSIONS AND RECOMMENDATIONS
The application is **Approvable.**

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/February 27, 2002

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Chem Review #4

DEC - 5 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.1 mg/0.02 mg (21 and 28 day regimens)

The deficiencies presented below represent **FAX** deficiencies.

A. Deficiencies:

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

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 specifications.

Sincerely yours,

/S/

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

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT JUL 31 2000

ANDA: 75-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.1 mg/0.02 mg (21 and 28 day regimens)

The deficiencies presented below represent **MAJOR** deficiencies.

A. Deficiencies:

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

2. Please provide a cGMP certification statement for the Facilities.

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

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 drug substance Levonorgestrel USP and Ethinyl Estradiol USP.

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

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

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).

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

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

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

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 %.

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.

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.

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.

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

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

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

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

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

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.

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

3. Please provide all accumulated room temperature stability to date.

Sincerely yours,

/S/

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

FEB 16

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-803

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.1 mg/0.02 mg (21 and 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. Please note that the holder, for DMF has not responded to Agency's deficiency letter dated June 26, 2000. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

2. Your response to comment 16 in the amendment dated September 7, 2000 is not satisfactory. Please revise the drug product release and stability specifications to add disintegration testing for placebo tablets.

3. Room temperature stability data at three months time point for levonorgestrel and ethinyl estradiol tablets, USP 0.1 mg/0.02 mg is missing on page 149 of the amendment dated September 7, 2000. Please explain.

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

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

2. The information submitted in all related DMFs should be adequate prior to the approval of the application.

Sincerely yours,

/S/

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