Appendix A: Medical Claims Indicators for Hepatic Disorders

ICD-9/CPT Code	Description
070	Viral hepatitis
570	Acute and subacute necrosis
571	Chronic liver disease and cirrhosis
572.2	Hepatic coma
572.4	Hepatorenal syndrome
573	Other disorders of the liver including
782.4	Jaundice unspecified, not newborn
789.1	Hepatomegaly
790.4	Nonspecific elevation of transaminase or
794.8	Abnormal liver function test
47000	Biopsy of liver, percutaneous
47001	Biopsy of liver with other procedure
47100	Wedge biopsy of liver
47133-47136	Liver transplant

Three-digit ICD-9 ranges include all 4- or 5-digit codes within each range

Medical Claims Indicators for Renal Dysfunction

ICD-9 codes 580.xx-589.xx

APPEARS THIS WAY
ON ORIGINAL

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

Sponsor Acceptance of Phase 4 Commitment Proposal, July 7, 2000.

Phase 4 studies desired by the Division; sponsor should commit to providing a full program/protocol to address these phase 4 commitments within 120 days of approval. Commitment in writing is required prior to approval.

- The first phase 4 commitment was for the sponsor to provide an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal/hepatic impairment or patients predisposed to hyperkalemia due to its potential antimineralocorticoid activity
- The second phase 4 commitment was a surveillance or evaluation program to evaluate the inappropriate prescribing of Yasmin to patients with underlying hepatic or renal dysfunction using a database of Yasmin users; the database would provide a list of all Yasmin users, and these patients would then be screened carefully for any past or recent diagnoses of hepatic and/or renal dysfunction; full case report summaries of all such inappropriate prescriptions, including patient outcome, would then be required.
- The third phase 4 commitment would be to use the same database to again evaluate all patients prescribed Yasmin for the subsequent outcome of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc (other search terms may also be considered appropriate); patients taking Yasmin and experiencing these types of events (or taking Yasmin within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.
- The fourth phase 4 commitment would be to analyze more carefully pregnancy outcomes which occur in patients exposed to Yasmin; this could be done in the same cohort of Yasmin users described in the database; in addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin exposure; a pregnancy exposure registry is an alternative; outcome on as many patients as possible is desired and may require several years of follow-up; finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended

Berlex acknowledges the Division's concerns with YASMIN as communicated during the teleconference on July 5, 2000. We agree to provide a full program/protocol to address the four Phase 4 commitments as described above within 120 days of approval.

We have reviewed the article cited by Dr. Marianne Mann of the Division during the teleconference which was published in the June 15, 2000 New England Journal of Medicine entitled, "Thrombotic Thrombocytopenic Purpura and Clopidogrel – A Need for New Approachee to Drug Safety". We agree to fufill the Phase 4 commitments through an active surveillance program in a meaningful sample of YASMIN users over an appropriate time period based on the principles described in this article.

We anticipate frequent dialogue with Divison representatives in order to finalize the details of the Phase 4 program/protocols.

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

DRUDP Phase 4 Commitment Proposals, July 5, 2000

/S/

7/10/00

APPEARS THIS WAY
ON ORIGINAL

- **Phase 4 studies desired by the Division; sponsor should commit to providing a full program/protocol to address these phase 4 commitments within 120 days of approval. Commitment in writing is required prior to approval.**

- The first phase 4 commitment was for the sponsor to provide an educational outreach program for health care providers and patients, focusing on Yasmin's contraindications in patients with renal/hepatic impairment or patients predisposed to hyperkalemia due to its potential antimineralocorticoid activity
- The second phase 4 commitment was a surveillance or evaluation program to evaluate the inappropriate prescribing of Yasmin to patients with underlying hepatic or renal dysfunction using a database of Yasmin users; the database would provide a list of all Yasmin users, and these patients would then be screened carefully for any past or recent diagnoses of hepatic and/or renal dysfunction; full case report summaries of all such inappropriate prescriptions, including patient outcome, would then be required.
- The third phase 4 commitment would be to use the same database to again evaluate all patients prescribed Yasmin for the subsequent outcome of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis, etc (other search terms may also be considered appropriate); patients taking Yasmin and experiencing these types of events (or taking Yasmin within one month of such events) would be considered concerning; full case reports summaries, including patient outcome, would be required for these patients.
- The fourth phase 4 commitment would be to analyze more carefully pregnancy outcomes which occur in patients exposed to Yasmin; this could be done in the same cohort of Yasmin users described in the database; in addition, the Organization of Teratogen Information Services (OTIS), or other resources could be used to collect data on all patients reporting a Yasmin exposure; a pregnancy exposure registry is an alternative; outcome on as many patients as possible is desired and may require several years of follow-up; finally, collecting all post-marketing adverse event reports and placing them in a format to help identify signals of developmental toxicity is recommended

NDA 21-098
Yasmin® 28 Tablets (drospirenone/ethinyl estradiol)
Berlex Laboratories, Inc.

There is no Press Office Information for this product at this time.

/S/

4/18/01

APPEARS THIS WAY
ON ORIGINAL

13. PATENT INFORMATION

Pursuant to 21 CFR 314.50(h)(ii), in the opinion of Berlex Laboratories, Inc., there are no patents that claim the combination of Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg, on which the investigations that are relied upon in this New Drug Application, NDA 21-098, were conducted, nor are there any patents that claim a use of the combination of Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg.

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to this New Drug Application for YASMIN™ [Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg] Tablets, NDA 21-098.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21098 SUPPL # ___

Trade Name Yasmin® 28 Tablets

Generic Name drospirenone/ethinyl estradiol

Applicant Name Berlex Laboratories, Inc. HFD-580

Approval Date May 11, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /X___/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Ethinyl Estradiol is the active moity found in the majority of the approved Oral Contraceptive Products. Examples:

NDA 19-697 ORTHO TRI-CYCLEN
NDA 20-071 Desogen
NDA 20-130 Estrostep
NDA 20-683 Alesse
NDA 20-713 Mircette

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the
(c) application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 92052

Investigation #2, Study # 96049

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /X___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X___/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1 Study # 92052

Investigation # 2 Study # 96049

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /X___/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /_X__/! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
5/11/01 03:14:29 PM

APPEARS THIS WAY
ON ORIGINAL

Statement of Claimed Exclusivity

Pursuant to 21 U.S.C. 355(j)(4)(D)(iii) and 21 U.S.C. 355(c)(3)(D)(iii), and with reference to 21 CFR 314.50(j)(1) and to 21 CFR 314.108(b)(4)(iv), Berlex Laboratories, Inc. hereby claims a period of 3 years marketing exclusivity for YASMIN™ [Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg] Tablets, the subject of New Drug Application, NDA 21-098. This request for a three-year exclusivity period is based upon the following criteria:

1. Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets has not been previously approved by the Food and Drug Administration.

2. Results of the two new clinical investigations, identified below, included in NDA 21-098 to support a finding of substantial evidence of effectiveness of Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets as an oral contraceptive for the prevention of pregnancy in women:

   A. Report 98180, Protocol 96049, An Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of a Monophasic Oral Contraceptive Preparation, Containing Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg", conducted in the US [redacted] Report 98180 can be found in NDA 21-098 in Volume 147 on page 8 38942.

   B. Report AI51, Study 92052, a multicenter, open-labeled, randomized study on cycle control and tolerance of SH T 470 FA in comparison with Marvelon® under long term contraceptive use", conducted in Europe. Report AI51 can be found in NDA 21-098 in Volume 60 on page 8 03525.

3. A determination that the two aforementioned clinical investigations are essential to the approval of Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets as an oral contraceptive for the prevention of pregnancy in women. Berlex Labratories, Inc. certifies that there are not sufficient published studies or publicly available reports of clinical investigations, other than those sponsored by Berlex Labratories and Schering AG, Berlin, Germany, the parent company of Berlex, to support the approval of NDA 21-098.

4. Berlex Laboratories, Inc. was the sponsor named [redacted] submitted to the Food and Drug Administration on October 7, 1996, for the investigation of Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets by the Division of Reproductive and Urologic Drug Products. In addition, Berlex Laboratories was the sponsor of the study conducted in the U.S. under Protocol 96049. Schering AG, the parent company of Berlex, was the sponsor of Study 92052 conducted in Europe. Both of these studies are essential to the approval of NDA 21-098.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel, Intellectual Property
US Representative of Schering AG

May 6, 1999
Date

Certification Under Section 306(k)(1) of the FD & C Act

Berlex Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-098 for YASMIN™ [Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg] Tablets.

APPEARS THIS WAY
ON ORIGINAL

BERLEX LABORATORIES, INC.

Joan Mutascio
Regulatory Submissions &
Information Associate

5/7/99
Date

gab\debarment\drspocbr

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 10, 2001

From: Kim Colangelo
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-098

I have reviewed the financial disclosure information submitted by Berlex Laboratories in support of their resubmission of NDA 21-098. This resubmission is intended to address deficiencies listed in the "approvable" letter from the Office of Drug Evaluation III dated July 10, 2000. Ms. Lana Pauls (see memo dated March 7, 2000) reviewed financial disclosure information from the original submission of this NDA. No new clinical trials were submitted in the first resubmission, therefore, no financial disclosure review was performed.

MAR 0 1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 6, 2000 LLP 3/7/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 21-098)

I have reviewed the financial disclosure information submitted by Berlex Laboratories in support of NDA 21-098. These documents are dated May 14, 1999 and March 3, 2000 (attached).

F

[redacted]

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

BERLEX

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

March 3, 2000

Susan Allen, M.D, MPH, Acting Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Request for Financial Disclosure

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product.

Reference is also made to a telephone conversation between Ms. Lana Pauls of the Division and the undersigned on February 23, 2000. During this conversation, Ms. Pauls informed the undersigned that financial disclosure information is needed for the foreign investigators. Ms. Pauls acknowledged the financial certification for the US study that appears in Item 19 of NDA 21-098. Ms. Pauls noted our statement that Berlex is working with our parent company, Schering AG, trying to obtain financial information for over 100 European investigators. In addition to these studies, Ms. Pauls requested that we update the financial disclosure form to include investigators for the renal impairment study. Ms. Pauls stated that the Division had elevated this study to pivotal status.

In response to Ms. Pauls' request, attached are two Forms FDA 3454. One form covers the two studies below:

Study Number	Report Number	Study Title
92052	A151	A multicenter, open-labeled, randomized study on cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 26 cycles under long term- contraceptive use
93044	AJ06	Study of cycle control and tolerance of SH T 470 FA in comparison with Marvelon® in up to 2100 healthy women over 13 cycles of contraceptive use

The second form covers the renal impairment study identified below. Since financial disclosure was already completed for the above studies prior to this request, another financial disclosure form was completed for the renal impairment study.

Study Number	Report Number	Study Title
303063	Not available	Open-label study to assess the effects of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days

All of these studies were conducted by our parent company, Schering AG, in Berlin, Germany

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez
Manager
Drug Regulatory Affairs

NFV/letter/drpoc062

Desk copy (cover letter): Ms. Lana Pauls
Ms. Jeanine Best

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See enclosure 1) for study no. 92052 (report no. AI51)*	*) Pivotal European Study
	See enclosure 2) for study no. 93044 (report no. AJ06)**	**) Major supportive safety and efficacy European Study

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
DR. RENATE HEITHECKER	INTERNATIONAL STUDY MANAGER, FEMALE HEALTHCARE
FIRM/ORGANIZATION SCHERING AG	
SIGNATURE 	DATE 24/02/2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages Redacted 11

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Confidential,
Commercial Information

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-098

DISCIPLINE REVIEW LETTER

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

DEC 12 2

Dear Ms. Velez:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yasmin™ 28 (drospirenone/ethinyl estradiol) Tablets.

We also refer to your submission dated November 14, 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

1. The Drug Master ——— for drospirenone has been found to be deficient. The DMF holder has been notified that approval of your application is contingent upon adequate information being provided in the DMF.

2. Your proposal to eliminate release testing for impurities is not acceptable for the following reasons:

   - Because only one out of 25 product lots per year will be placed on stability study, no information on impurities would be available for the majority of market product lots. The testing for impurities is necessary in order to avoid the release of a drug product lot that has exceedingly high levels of these components and/or that might exceed the shelf-life specifications during the expiration dating period.

   - Without impurity data at release, it would be difficult to be alerted to any unexpected problem in the manufacturing process or to validate any post-approval change in the manufacturing process.

   At minimum, testing for Total Impurities should be performed prior to the release of every product lot. The release specifications should be ≤ 5.0% Total Impurities for ethinyl estradiol and ≤ 0.5% Total Impurities for drospirenone.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 12 2

Schering AG
Attention: Dr. S. Ode Hakim
Dossier Management
D-13342 Berlin
Germany

Dear Dr. Hakim:

Your letter dated April 30, 1999, authorizes us to reference Drug Master [redacted] for Drospirenone in support of Berlex Laboratories, Inc's., new drug application (NDA 21-098).

Your communication dated November 6, 2000, was reviewed in support of this NDA. Since approval of Berlex Laboratories, Inc's. NDA is contingent upon adequate information being provided in a supporting DMF, please submit the following information as soon as possible:

1. [redacted]

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: CENTRAL DOCUMENT ROOM
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Berlex Laboratoies, Inc. will be notified that the information in your DMF is inadequate to support their NDA. When you amend your [redacted] please notify Berlex Laboratories, Inc. in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that the DMF has been amended. Do not provide a copy of the amendment to the review chemist.

Suong Tran, Ph. D
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, you may contact Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival DMF (2 copies) 12138
DIVISION FILE for NDA 21-098
HFD-580/JBest
HFD-580/Tran/Rhee
Drafted: JAB/December 7, 2000
final: JAB/December 12, 2000
concurrence: Rumblet,12.07.00/Tran,12.08.00/Rhee,12.08.00/Allen,12.11.00
filename:

DMF DEFICIENCY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-098

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

DEC 07 2000

Dear Ms. Velez:

We acknowledge receipt on November 13, 2000 of your November 9, 2000 resubmission to your new drug application (NDA) for Yasmin™ 28 (drospirenone/ethinyl estradiol) Tablets.

This resubmission contains: additional study data to assess the risk of hyperkalemia in women using Yasmin™ 28 Tablets; a revised Phase 4 Program; revised draft labeling to reflect new clinical data; a Safety Update Report; and revised carton labels.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is May 13, 2001.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-098

MAY 24 2000

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

We acknowledge receipt on May 10, 2000 of your May 9, 2000 resubmission to your new drug application (NDA) for Yasmin® (drospirenone/ethinyl estradiol) .

This resubmission contains additional clinical information related to the effects of Yasmin® in renally-impaired patients, and revised labeling that contains appropriate information from the renal impairment study, submitted in response to our March 17, 2000 action letter.

With this amendment, we have received a complete response to our March 17, 2000 action letter.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 21-098

DEC 16 1999

INFORMATION REQUEST LETTER

Berlex Laboratories, Inc.
Attention: Nancy Velez
Manager, Drug Regulatory Afairs
340 Changebridge Road
P. O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your May 14, 1999 new drug application for Yasmin™ (drospirenone/ethinyl estradiol) Tablets.

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Please provide certificates of analysis of the drug substance batches (#'s 80301, 80302, and 80303) that were used in the manufacture of the drug product batches SHT470FA.
2. Please provide specifications and analytical methods if acceptance (confirmatory) testing of drug substance batches is performed upon receipt at the drug product manufacturing site.
3. Please provide the name and address of the facility used for acceptance (confirmatory) testing of raw materials, including drug substances and excipients.
4. When the desired weight of the drug substance is calculated, the assay result of the drug substance batch is entered into the calculation. Please clarify whether the assay result is taken from the certificate of analysis of the drug substance batch or if it is from a confirmatory assay test performed on the batch at the drug product manufacturing site.
5. Please provide information on the compatibility between the [redacted] (for packaging tablets in bulks) and the coated tablets. In addition, please provide appropriate references to indirect food additive regulations (21 CFR 174-186) or other safety information on the bag materials.
6. Please indicate storage conditions and the length of time that elapses between the completed manufacture of uncoated tablets (tablet cores) and the coating process.
7. Please indicate storage conditions and the length of time that elapses between the completed manufacture of coated tablets and the final packaging into blister packs.
8. Please provide a narrative and diagram for the complete packaging process (from tablet packaging into a blister pack to carton packaging with patient and physician inserts).

9. Please provide release specifications that include testing for impurities and degradation products.
10. Please lower the limit for unidentified degradants of drospirenone to reflect available stability results; 0.5% is too high. According to ICH Q3B, such a limit would require a structural characterization of the impurity; therefore, an unidentified impurity cannot have a limit of 0.5%.
11. Please tighten the limits for the iso-compound and total impurities of drospirenone to reflect available stability results.
12. Please lower the limits of ethinyl estradiol and drospirenone for Absence of ethinyl estradiol and drospirenone in placebo tablets. The specifications for this testing should be non-detectable for either drug substance with respect to the limits of detection of the HPLC test method.
13. [redacted]
14. Regarding the HPLC test method for Assay of ethinyl estradiol and drospirenone (content determination), Content Uniformity, and Degradation of drospirenone:
    a. The operating temperature should be indicated for the HPLC system described on page 4:4.715.
    b. Sample information and peak assignment for the chromatograms 5-6 on page 4:4.718 should be provided.
    c. This test method should be validated for the determination of degradation of drospirenone.
15. Please provide a validation report regarding the HPLC test method for absence of ethinyl estradiol and drospirenone.
16. Please provide the complete 12-month stability data, a proposed shelf-life for Yasmin™ Tablets, and a post-approval stability protocol.
17. Please revise the pouch and carton labels to read: "drospirenone and ethinyl estradiol"
18. Please revise the storage statement on the carton label to "Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)" [see USP Controlled Room Temperature]". In addition, the carton label should be revised with the following suggested language:

    "1 Carton containing 3 units, each unit consisting of 1 pouch-enclosed blister of 21 (28) tablets. Each yellow tablet contains..."

    "To the Dispenser: Each of the 3 units in this carton contains two pieces of information..."

    "Manufactured for Berlex Laboratories, Wayne, NJ 07470 by Schering GmbH, Germany".
19. Please revise the blister and pouch labels to read: "Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)". Please include the lot number, and expiration date on the backside of the blister label and include: "Distributed by Berlex Laboratories, Wayne, NJ 07470" or "Manufactured for Berlex Laboratories, Wayne, NJ 07470 [redacted]

20. Each carton contains three units (boxes/cartons), each consisting of the brief and detailed patient package inserts, the day label, and one pouch containing one blister pack of tablets. Please provide the label for the unit (box/carton). The label text should be similar to that of the carton label.

If you have any questions, contact Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Div. Files
HFD-580/JBest
HFD-580/Rarick/Mann/Rhee/Tran/Rumble
HFD-820/DNDC Division Director JGibbs/SKoepkes
DISTRICT OFFICE
Drafted by: JAB/December 14, 1999
Initialed by:Rumble,12.14.99/Tran,12.14.99/Rhee,12.15.99/Mann,12.15.99/Rarick12.16.99
final: JAB,December 16, 1999
filename:

INFORMATION REQUEST (IR)

Number of Pages Redacted 4

❖❖❖

Confidential,
Commercial Information

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-098

Berlex Laboratories, Inc.
Attention: Ms. Nancy Velez
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

JUL 20 1999

Dear Ms. Velez:

Please refer to your pending May 17, 1999, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Yasmin™ (drospirenone/ethinyl estradiol) tablets.

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests:

1. To support the changes in composition and equipment in the to-be-marketed formulation, please provide comparative *in vitro* dissolution profiles of the clinical trial formulation (SH T 470FA) and the to-be-marketed formulation (SH T 470FA final) in multiple media (Case C profiles as per SUPAC IR guidance).

2. Please clarify which formulation was used in the supportive trial AJ06.

3. Please provide a complete report on the analytical method validation for drospirenone assay, including cross reactivity information.

4. Please provide the individual data supporting the mean quality control parameters and calibration curves for the assay of drospirenone and ethinyl estradiol in each pharmacokinetics study report.

5. Please provide a summary of human pharmacokinetics and bioavailability, individual study synopses, raw data analyzed in the pharmacokinetics studies and labeling in electronic format.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information

reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 7/22/99

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-098
HFD-580/Div. Files
HFD-580/J.Mercier/Rumble
HFD-580/Rarick/Mann/Jarugual/Parekh
HFD-820/DNDC Division Director (only for CMC related issues)
DISTRICT OFFICE

Drafted by: JM/June 30, 1999
Initialed by: Rarick7.13.99/Mann7.9.99/Rumble7.1.99/Parekh7.8.99/Jarugula7.1.99
final: July 20, 1999
filename ————

INFORMATION REQUEST (IR)

NDA 21-098

Berlex Laboratories, Inc.
Attention: Nancy F. Velez
Manager, Regulatory Affairs
340 Cambridge Road
P.O. Box 1000
Montville, NJ 07045-1000

MAY 19 1999

Dear Ms. Velez:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Yasmin (drospirenone 3mg/ethinyl estradiol) Tablets

Therapeutic Classification: Standard (S)

Date of Application: May 14, 1999

Date of Receipt: May 17, 1999

Our Reference Number: 21-098

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 13, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 14, 2000 and the secondary user fee goal date will be May 14, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We

will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-098
HFD-580/Div. Files
HFD-580/J.Mercier
HFD-580/Rarick/Mann/Allen/Slaughter/Safran/jordan/Raheja/Rhee/Mitra/Parekh/Jargula
DISTRICT OFFICE

Drafted by: JM/May 18, 1999
Initialed by:
final:
filename:

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL BERLEX

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

May 11, 2001

Susan Allen, M.D, MPH, Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NEW CORRESP
N-C

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Revised Physician Package Insert, Acceptance of Phase IV Commitments

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter. Seven Clinical Information Request Letters were received beginning in December of 2000 through May 4, 2001 requesting additional information to continue review of the NDA. Berlex responses were submitted from January 5, 2001 through May 7, 2001.

Reference is also made to the Division and Office of Drug Evaluation III edits on our most recent DRAFT labeling of May 9th which were received on May 10th and today. Also received today were comments on our Phase IV program which was submitted to the Division on November 6, 2000. These edits and Phase IV comments were discussed in two teleconferences held today.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

C DATE

As agreed during today's teleconferences, this submission contains the following:

Revised Physician PI

A revised electronic Physician Package Insert (includes Brief Summary Patient Package Insert and Detailed Patient Package Insert), reflecting our final changes, is provided in Attachment 1. The Physician PI is provided in Microsoft® Word 97 SR-1 format on one 3.5 inch diskette labeled "YASMIN® 28 TABLETS Physician PI" dated May 11, 2001. Marked as well as unmarked versions of the Physician PI are provided. Hard copies of the marked and unmarked versions are included immediately following the diskette in Attachment 1.

Berlex Laboratories certifies that the diskette provided herewith was scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created on May 2, 2001.

Acceptance of Phase IV Commitment

This letter serves as documentation that Berlex agrees to the Phase 4 commitments as outlined in the telefax and email of May 11, 2001 (see copy of May 11th communication provided in Attachment 2) with the following clarifications:

1. As agreed during the teleconference, the fourth bullet point in Comment 3 will be moved to appear as the fourth bullet point under Comment 1.

2. The database described in Comment 3 is the database described in our November 6, 2000 submission which contained our Phase IV program.

Should you require any additional information or have any questions regarding today's submission, please call the undersigned immediately at (973) 487-2305. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

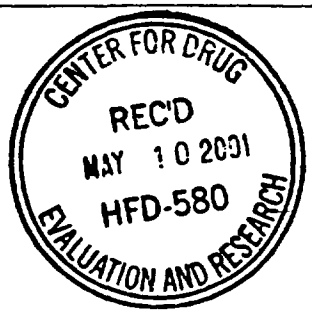
Nancy E. Velez
Manager
Drug Regulatory Affairs

Desk copies: Dr. Florence Ho
Dr. Scott Monroe
Ms. Jeanine Best

NFV/letter/drpoc190

TELEFAX
UPS OVERNIGHT

BERLEX



Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

May 9, 2001

ORIGINAL

Susan Allen, M.D., MPH, Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA ORIG AMENDMENT ORIGINAL

NDA ORIG AMENDMENT

N - PL

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Other: Revised Physician Package Insert

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter. Seven Clinical Information Request Letters were received beginning in December of 2000 through May 4, 2001 requesting additional information to continue review of the NDA. Berlex responses were submitted from January 5, 2001 through May 7, 2001.

Reference is also made to the Division and ODE III Label Edits on our most recent DRAFT Physician Package Insert (PI) of November 6, 2000. These edits were forwarded to Berlex by Jeanine Best of the Division on May 8, 2001 via the Internet and telefax. Additional reference is made to the teleconference held on May 9th between Berlex and Division and ODE III representatives to discuss these edits. Following discussion of the edits, it was agreed that Berlex would forward via the Internet and by telefax a revised Physician PI to Ms. Best by the end of the day for the Division and ODE III's immediate review. Ms. Best also requested a list of the Berlex representatives attending the teleconference.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

1. Attached please find a hard copy of the revised Physician PI consisting of 38 pages and dated May 9, 2001. This document is also being sent via the Internet today, protected by the same password used previously. In accordance with previous procedure, a marked as well as unmarked version of the Physician PI are provided. Edits are underlined in the marked, hard and telefax copies. In the Internet copy, edits in the marked copy are highlighted in yellow and underlined.

   All edits are self-explanatory. Please note that with regard to the Trussel table comment on page 6, Berlex has elected not to include footnotes 9 and 10 on Emergency Contraception Pills and Lactational Amenorrhea Method based on a previous agreement for LEVLITE® tablets (approved July 13, 1998). Approved labeling for both LEVLITE® and MIRENA® [(levonorgestrel-releasing intrauterine system) approved December 6, 2000] do not include these footnotes.

2. The following Berlex representatives attended today's teleconference:

   Don Atkinson - Vice President, Female Healthcare
   June Bray - Vice President, Drug Regulatory Affairs
   Sharon Brown - Director, Drug Regulatory Affairs
   Marie Foegh - Medical Director, Clinical Research & Development, Female Healthcare
   Jeff Frick - Strategic Business Director
   Nancy Konnerth - Manager, Advertising and Labeling
   Louise Palma - Manager, Clinical Data Management, Clinical Operations
   Harji Patel - Associate Director, Statistics, Female Healthcare
   Nancy Velez - Manager, Drug Regulatory Affairs
   Paul Zhang - Senior Staff Statistician, Female Healthcare

We are immediately available to discuss any comments you may have regarding the attached revised labeling. We look forward to hearing from you as soon as possible so that we can obtain approval on May 11, 2001.

Should you require any additional information or have any questions regarding this submission, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES

Nancy F. Velez

Nancy F. Velez
Manager
Drug Regulatory Affairs

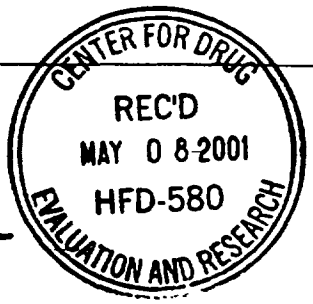
NFV/letter/drpoc175

Desk copy: Ms. Jeanine Best
Dr. Florence Ho
Dr. Scott Monroe

NDA ORIG AMENDMENT

BERLEX

TELEFAX
UPS OVERNIGHT



May 7, 2001 ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Susan Allen, M.D, MPH, Director
DIVISION OF REPRODUCTIVE AND UROLOGIC
DRUG PRODUCTS, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA-BIM

Dear Dr. Allen:

Re: NDA 21-098 – YASMIN® 28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Telephone Request of May 2, 2001

Reference is made to NDA 21-098 submitted on May 14, 1999 for YASMIN® 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 mg Tablets], an oral contraceptive (OC) product. An approvable letter was issued for this NDA on March 17, 2000. Our May 8 and 9th submissions constituted a complete response to this approvable letter. A second approvable letter was issued on July 10, 2000. Our November 6, 2000 clinical amendment provided a complete response to the July 10, 2000 approvable letter.

Reference is also made to a telephone conversation on May 2, 2001 between Ms. Jeanine Best of the Division and the undersigned. Ms. Best requested additional information for three cases listed on the following page of women who experienced adverse events while taking Yasmin in Germany. These AEs came to our attention as spontaneous, postmarketing reports from our parent company, Schering AG, Berlin, Germany and were recently submitted as !

Ms. Best's request is provided first in bold, followed by our response.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE