

The stability of drospirenone in serum samples was determined separately. Serum samples were spiked with 0.2, 1.0 and 3.2 ng drospirenone/ml and stored at approximately -20°C. Aliquots were thawed at different times as indicated in Tables 1 and 2 in Attachment 6 and were analyzed using the radioimmunological method described. The results show that drospirenone is stable in serum samples stored at about -20°C over a period of 22 months.

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.

The individual quality control data measured for drospirenone and ethinyl estradiol in the eleven pharmacokinetics studies described in Item 6 of the original NDA, with the exception of data from Report 9482², are provided in Attachment 7. They are ordered by report number and compound (analyte), in the order that the reports appear in the original NDA. For your reference, a list of the report numbers and their titles precede the individual data. Within each report, blue pages have been added to separate the compounds DRSP and EE, where appropriate.

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.

- a) Diskette #1, labeled "DRSP 3 mg/EE 0.03 mg Tablets Human PK and BA Summary" and dated November 18, 1999, contains the summary of human pharmacokinetics and bioavailability item which includes the individual study synopses. This is the most updated version of the summary including the formulation corrections. The file is identified as

contains 133 pages. Diskette #1 is provided in Attachment 8.

- b) Diskette #2, labeled "DRSP 3 mg/EE 0.03 mg Tablets Raw PK Data" and also dated November 18, 1999, contains the raw data for the following eight studies submitted in the original NDA:

8235	A470
6737	9776
A951	9274
A733	A198

Please note that these studies were chosen as a result of Dr. Jarugula's statement during the teleconference on August 18ⁿ for Berlex to decide which studies it considers important and to submit the raw data for those studies. The raw data sets provided include the studies involving evaluation of the absolute and relative bioavailability, bioequivalence, single and multiple dose pharmacokinetics, pharmacokinetic linearity, food effect and the evaluation of a potential pharmacokinetic interaction of DRSP with ethinyl estradiol. The files are also zipped and are provided in Microsoft® Excel 97 SR-1 format. They are identified by report number and are self-explanatory.

² It was decided during the August 18ⁿ teleconference that it is not necessary to submit these data from this percutaneous absorption study.

³ During the teleconference on August 18ⁿ, Dr. Jarugala told Berlex that zipped files would be acceptable.

Diskette #2 is provided in Attachment 9. Also included in this attachment, for your convenience, are hard copies of the raw data Excel worksheets for the eight studies. These worksheets are arranged by report number, in the order that the reports are presented in the original NDA. For your reference, a list of the report numbers and their titles precede the worksheets.

- c) Diskette #3, labeled "DRSP 3 mg/EE 0.03 mg Tablets PI" and also dated November 18, 1999, contains the Physician Insert that was submitted in the original NDA, which is the current version of the labeling. During the August 18th teleconference in response to Berlex's question, Dr. Jarugula requested that the labeling be unannotated rather than annotated. Ms. Mercier asked that a copy without annotations also be provided for her. The labeling on Diskette #3 is unannotated and is provided in Microsoft® Word 97 SR-1 format. The file name is _____ An additional and exact copy of this labeling has been included for Ms. Mercier on Diskette #4. These two diskettes are provided in Attachment 10.

Please note that our proposed trade name, YASMIN™, appears throughout the labeling. We are awaiting notification that the Labeling and Nomenclature Committee has approved the name.

Berlex Laboratories certifies that the four diskettes included in this submission have been scanned for viruses and are virus free using Network Associates VirusScanNT 4.0.3a created September 29, 1999.

We trust that the information provided in this submission addresses all of your concerns and will enable you to complete the review of the NDA. 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/drproc131

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED	
CSO ACTION	<input type="checkbox"/> MEMO
<input type="checkbox"/> LETTER	
CSO #	DATE

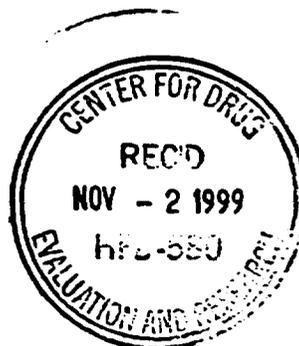
NC

November 1, 1999

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Jeanine Best, Project Manager
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 Ms. Best:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Additional Desk Copy of ISS and ISE

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to a voice mail communication today from you to the undersigned requesting an additional desk copy of the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE).

Per your request, one desk copy of the ISS, consisting of 425 pages, and one desk copy of the ISE, consisting of 98 pages, are attached. Two separate volumes are provided. The original NDA pagination appears in the bottom right hand corner of each page.

Should you have any additional requests, please feel free to call me at (973) 276-2305. My fax number is (973) 276-2016.

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

NFV/letter/drproc137

Sincerely,

BERLEX LABORATORIES

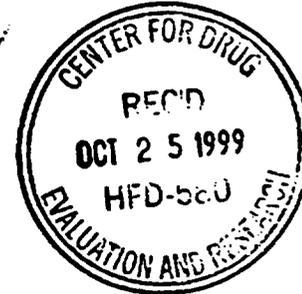
Nancy F. Velez
Manager
Drug Regulatory Affairs

155
October 22, 1999

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Jeanine Best, Project Manager
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 Ms. Best:

**Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Response to FDA Request for Information:
Mouse Carcinogenicity Tumor Data**

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to a telephone conversation between you and Berlex representatives, Ms. Nancy Bower and the undersigned on September 28, 1999. During this telephone conversation Berlex was requested to provide clarification regarding coding of the mouse carcinogenicity tumor data. Specifically, Berlex was informed that Dr. Mohjee Ng, the statistician, thought that the coding appeared to be incorrect for the control group in file _____ This data was submitted via diskette on September 14, 1999. Ms. Bower agreed to contact the contract research organization (CRO) that was responsible for reporting the mouse carcinogenicity study.

Additional reference is made to the submission dated September 30, 1999 which provided clarification of the coding for the mouse carcinogenicity tumor data. On October 4, Ms. Best called and spoke with S. Brown and N. Bower of Berlex. Ms. Best informed Berlex that Dr. Ng was still having difficulty with the mouse carcinogenicity tumor coding.

Ms. Best was informed that Berlex would contact the responsible CRO again and request that the data be recoded to assure consistency among the control group.

On October 13, Ms. Best was informed that Berlex hopes to have the re-coded data during the week of October 18.

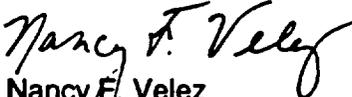
Berlex is providing as an appendix an electronic file of the recoded *mouse* carcinogenicity. The electronic file contains a new tumor code file and the recoded tumor data for Groups 8-10. The tumor code file contains codes for approximately eight additional tumors which were only seen in the group 8-10 animals. The files are exactly the same in all other respects to the previous file. Because additional tumors are coded for in this file, this file should be used to provide tumor code information for all study groups. Also provided in the appendix in hard copy is a code sheet describing the records and fields in the dataset and a printout of the first 70 records of the data.

Berlex Laboratories certifies that the attached diskette has been scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created September 1, 1999.

Berlex hopes this response finally satisfies Dr. Ng's request for clarification of the tumor coding for the mouse carcinogenicity. However, if it does not, please contact me should you require any additional information or have any questions regarding this submission. You can call me at (973) 276-2305 and my telefax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES



Nancy F. Velez

Manager

Drug Regulatory Affairs

NFV/letter/drdoc132

APPEARS THIS WAY
ON ORIGINAL

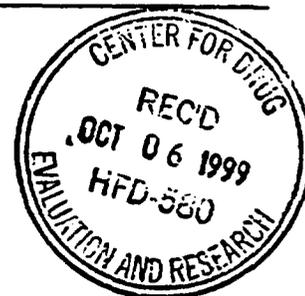
REVIEWS COMPLETED	
REVISION:	NO
REASON: <input type="checkbox"/> INITIAL	NO
INITIALS	DATE

Drug Development & Technology
Division of Berlex Laboratories, Inc.

September 30, 1999

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

Jeanine Best, Project Manager
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 Ms. Best:

**Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
Response to FDA Request for Information:
Mouse Carcinogenicity Tumor Data**

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to a telephone conversation between you and Berlex representatives, Ms. Nancy Bower and the undersigned on September 28, 1999. During this telephone conversation Berlex was requested to provide clarification regarding coding of the mouse carcinogenicity tumor data. Specifically, Berlex was informed that Dr. Mohjee Ng, the statistician, thought that the coding appeared to be incorrect for the control group #003. This data was submitted via diskette on September 14, 1999. Ms. Bower agreed to contact the contract research organization (CRO) that was responsible for reporting the mouse carcinogenicity study.

In response to Dr. Ng's request, Berlex received the following information from the CRO concerning the electronic data for the study:

"The data for the study was captured onto two different computer protocols due to the large number of groups on the study. Groups 1-7 were on one computer protocol and Groups 8-10 were on another computer protocol.

The group identification in the files (the third column of figures) and the group that Dr. Ng refer to are indicated below."

File Name	Group identification in file	Study group number
	0	1
	1	2
	2	3
	3	4
	4	5
	5	6
	6	7
	0	8
	1	9
	2	10

"Within each computer protocol each finding is given a code number, which will be unique to that computer protocol but will not necessarily be unique within the FDA files for the whole study. Therefore, the files which include 'Groups8-10' in the file name must be compared with each other and not with the files with 'Groups1-4' or 'Groups5-7' in the file names."

For further clarification, Berlex is providing the following additional information:

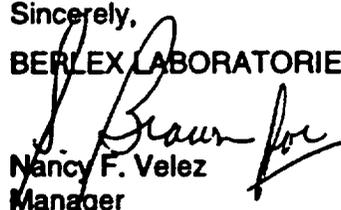
"The same finding for a different tissue is given a different code number; for example, for Groups 8-10 the codes 470 and 143 indicate adenoma. The code 470 is for adenoma in the pituitary and 143 is the code for adenoma in the Hardarian gland.

The tumor code of 000 is a default code used to indicate that the tissue had not been examined, for example, due to autolysis, or a missing tissue. The system is required to know how many tissues have been examined and by identifying the tissues that have not been examined, this is possible."

Berlex hopes this response satisfied Dr. Ng's request for clarification of the tumor coding for the mouse carcinogenicity. However, if it does not, please contact me should you require any additional information or have any questions regarding this submission. You can call me at (973) 276-2305 and my telefax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES


Nancy F. Velez
Manager
Drug Regulatory Affairs

September 22, 1999

Drug Development & Technology

Division of Berlex Laboratories, Inc.

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

Jeanine Best, Project Manager
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 Ms. Best:

**Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Mouse Carcinogenicity Data on Diskette**

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to telephone communications between Jennifer Mercier and Dr. Krishan Raheja of the Division, Mohjee Ng of the Division of Biostatistics and the undersigned on September 1, 3, 7 and 13, 1999. The outcome of these communications was that Mohjee Ng needed an electronic copy of the mouse carcinogenicity data.

Additional reference is made to our submission of September 14, 1999 which contained the electronic desk copy of the mouse carcinogenicity data.

On September 21, 1999, you informed the undersigned via a voice mail message that you needed another diskette of the mouse carcinogenicity data because the one sent on September 14th had been lost in your interoffice mail.

Per your request, an additional electronic desk copy of the mouse carcinogenicity data is attached for Mohjee Ng. Berlex Laboratories certifies that the attached diskette has been scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created September 1, 1999.

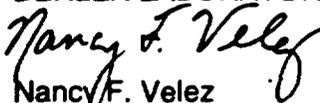
As described in the September 14th submission, these mouse carcinogenicity data were submitted to _____ in both hard copy and electronic format as a Response to FDA Request/Information Amendment on November 5, 1998 (Serial No. 024). A hard copy

of the mouse carcinogenicity report, Report AZ86 entitled, "ZK 4944¹ and ZK 30595² – Oncogenicity Study by Oral Gavage Administration to Female CD-1 Mice for 104 Weeks", was also submitted in Item 5 of NDA 21-098 (Vols. 15 - 21, beginning on page 5 04194).

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/drpc120

**APPEARS THIS WAY
ON ORIGINAL**

¹ Ethinyl Estradiol

² Drospirenone



September 14, 1999

Drug Development & Technology
Division of Berlex Laboratories, Inc.340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 276-2000

Jennifer Mercier, Project Manager
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 Ms. Mercier:

Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
OTHER: Mouse Carcinogenicity Data on Diskette

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to telephone communications between you and Dr. Krishan Raheja of the Division, Mohjee Ng of the Division of Biostatistics and the undersigned on September 1, 3, 7 and 13, 1999. The outcome of these communications is that Mohjee Ng needs an electronic copy of the mouse carcinogenicity data.

As communicated to you, these mouse carcinogenicity data were submitted to _____ in both hard copy and electronic format as a Response to FDA Request/Information Amendment on November 5, 1998 (Serial No. 024). A hard copy of the mouse carcinogenicity report, Report AZ86 entitled, "ZK 4944¹ and ZK 30595² – Oncogenicity Study by Oral Gavage Administration to Female CD-1 Mice for 104 Weeks", was also submitted in Item 5 of NDA 21-098 (Vols. 15 - 21, beginning on page 5 04194).

Per your request, an additional electronic desk copy of the mouse carcinogenicity data is attached for Mohjee Ng. Berlex Laboratories certifies that the attached diskette has been scanned for viruses and is virus free using Network Associates VirusScanNT 4.0.3a created September 9, 1999. You informed me that an additional hard copy of the report is not needed.

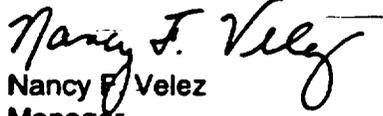
¹ Ethinyl Estradiol

² Drospirenone

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/dr poc113

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

**APPEARS THIS WAY
ON ORIGINAL**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

ORIGINAL
ORIG AMENDMENT
BC

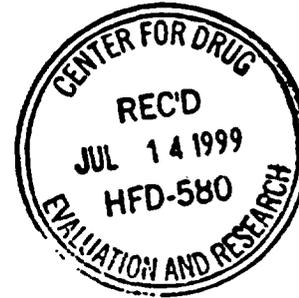
BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

July 8, 1999

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

Lisa Rarick, M.D., 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. Rarick:

**Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
AMENDMENT TO PENDING APPLICATION**

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 Tablets], an oral contraceptive (OC) product.

Reference is also made to telephone communications between Dr. Amit Mitra of the Division and the undersigned on July 1 and 2, 1999. The Office of Compliance had contacted Dr. Mitra regarding the site being used for the micronization of ethinyl estradiol (EE). Specifically, they requested confirmation that the micronization of EE had been transferred from the _____

_____ The Office of Compliance understood that micronization had not been done at the _____ site for years.

The undersigned confirmed for Dr. Mitra that the micronization of EE was transferred from the _____ site. The undersigned also informed Dr. Mitra that, erroneously, only the _____ had been identified in Item 4 of the NDA. Both the _____ sites should have been listed as some batches of EE may have been micronized in _____ up until the second quarter of 1997. Dr. Mitra requested that the affected pages in the NDA be corrected, telefaxed to him and submitted as an amendment to the NDA. The only affected page, page 4 – 7, has been corrected and is attached. This page was telefaxed to Dr. Mitra today under separate cover.

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/drdoc087

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

May 14, 1999

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Lisa Rarick, M.D., 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. Rarick:

**Re: NDA 21-098 – YASMIN™ 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 Tablets)
ORIGINAL NEW DRUG APPLICATION**

Pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50, Berlex Laboratories, Inc. is submitting herewith a New Drug Application for YASMIN™ 21/28 TABLETS [Drospirenone (DRSP) 3 mg and Ethinyl Estradiol (EE) 0.030 Tablets], an oral contraceptive (OC) product.

DRSP is a novel progestin, a derivative from 17 α -spiro lactone which, like natural progesterone, possesses progestogenic and aldosterone-antagonistic properties. In addition, it is anti-androgenic and is devoid of any androgenic, estrogenic, and glucocorticoid activity. The combination of these characteristics clearly differentiates DRSP from all other currently marketed progestins.

The clinical development program of DRSP 3 mg/EE 0.030 mg was discussed in a Phase 3 meeting between representatives of Berlex and the FDA Division of Reproductive and Urologic Drug Products on February 12, 1997 and was considered adequate to satisfy the Agency's "Guideline for Preclinical and Clinical Testing of Steroidal Contraceptives". This was confirmed in a Pre-NDA meeting with the Division on January 28, 1999. Division minutes for both of these meetings are provided immediately following this cover letter.

¹ The Division informed Berlex in the Pre-NDA meeting held on January 28, 1999 that the proposed tradename YASMIN has been submitted to the Labeling and Nomenclature Committee for consideration.

As discussed, the safety and efficacy data in this NDA for DRSP 3 mg/EE 0.030 mg were obtained from two pivotal efficacy and safety studies: 1) Report AI51 (Study 92052), conducted in Europe by our parent company, Schering AG, Berlin, Germany, which used Desogen (European tradename "Marvelon") as a comparator and 2) Report 98180 (Study 96049), an uncontrolled study conducted in the US under Berlex. These studies were designed to comply with the "Guideline for the Preclinical and Clinical Testing of Steroidal Contraceptives". It was agreed that the number of reported cycles and size of the safety database will support the filing of the NDA.

In addition to the two pivotal studies, this NDA includes 33 supportive clinical studies. These studies confirmed that YASMIN™ appears to be a well tolerated, safe and effective OC. The overall results of the two pivotal studies alone yield an uncorrected Pearl Index of 0.40 and a corrected Pearl Index of 0.41. The uncorrected Pearl Index for all efficacy studies was 0.54 and corrected was 0.55.

This NDA is comprised of a 430 volume Archival Copy and a 307 volume Review Copy that includes five technical sections.

The application provides for the YASMIN™ commercial product packaged in two presentations: a 21-day blister pack containing only active tablets; and a 28-day blister pack containing 21 active tablets and 7 inert (placebo) tablets. To date, DRSP 3 mg/EE 0.030 mg tablets have not been marketed anywhere in the world.

CMC DOCUMENTATION

Drug substance information for both drospirenone and ethinyl estradiol is provided in the Type I Drug Master Files. Letters authorizing the Agency to refer to these DMFs are provided in Item 4 of the application.

Reference is made to the Phase 3 meeting of February 12, 1997 between Berlex and the Division wherein it was agreed that it would be acceptable for Berlex to submit 6-month drug product stability data with the understanding that Berlex will amend the NDA with 12-month stability data during the review process.

ELECTRONIC SAS DATASETS

At the January 28, 1999 Pre-NDA meeting, representatives of the Division of Reproductive and Urologic Drug Products requested an efficacy SAS dataset (see Attachment 2 of the Division minutes of the meeting that are included with the dataset).

Based on previous experience with this Division, we are including with this submission one copy of the requested SAS dataset on one, 3.5 inch diskette for the reviewing statistician. A hard copy of these data will be available upon request.

Included with the diskette is a document entitled, "SAS Dataset Documentation for the DRSP/EE OC NDA", which explains the content of the SAS dataset and provides instructions for its manipulation. The dataset includes data from the 10 clinical studies determined by the Sponsor to be critical to the evaluation of contraceptive efficacy of the DRSP 3 mg/EE 0.03 mg tablet that are provided in Item 10, Statistical Section.

Berlex Laboratories certifies that the diskette has been scanned for viruses and is virus free using VirusScan NT created March 29, 1999. The diskette is provided in a binder identified as "Electronic SAS Datasets" which includes a copy of this cover letter, a copy of the Division minutes and the explanation of the dataset described above.

CLAIMED EXCLUSIVITY

Berlex is claiming a period of 3 years of marketing exclusivity for YASMIN™. A "Statement of Claimed Exclusivity" has been included in Item 14, Patent Certification.

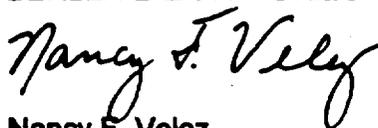
FINANCIAL CERTIFICATION

A statement regarding financial certification, as described in Regulation 21 CFR 54 which became final on February 2, 1999, is provided in Item 19, Other.

Please call me at (973) 276-2305 to answer any questions regarding this submission. My fax number is (973) 276-2016.

Sincerely,

BERLEX LABORATORIES



Nancy F. Velez
Manager
Drug Regulatory Affairs

Desk Copy: Ms. Jennifer Mercier

NFV/letter/dr poc064

**APPEARS THIS WAY
ON ORIGINAL**

**Number of Pages
Redacted 1**



Confidential,
Commercial Information

MEMORANDUM OF TELECON

DATE: May 11, 2001

APPLICATION NUMBER: NDA 21-098

BETWEEN:

Name: Nancy Velez, Manager, Drug Regulatory Affairs
Phone: (973) 487-2305
Representing: Berlex Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Final Labeling Revision

Please revise the Detailed Patient Package Insert, **GENERAL PRECAUTIONS 1. Missed periods and use of oral contraceptives before or during early pregnancy** section as follows:

...“Nevertheless, oral contraceptives _____ should not be used during pregnancy

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Jeanine Best
5/14/01 11:51:00 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Teleconference Meeting Minutes

Date: May 11, 2001

Time: 1:30-2:00 PM

Location: Parklawn; 13-B45

NDA 21-098

Drug: Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling

Meeting Chair: Dr. Florence Houn

External Lead: Ms. June Bray

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:

Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)

Dena Hixon, M.D., Clinical Team Leader, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Berlex Laboratories, Inc.

June Bray, Vice President, Drug Regulatory Affairs

Don Atkinson, Vice President, Female Healthcare

Sharon Brown, Director, Drug Regulatory Affairs

Marie Foegh, M.D., Medical Director, Clinical Research and Development, Female Healthcare

Jeff Frick, Strategic Business Director

Nancy Velez, Manager, Drug Regulatory Affairs

Meeting Objective: To discuss final labeling recommendations and provide final Phase 4 commitment comments.

Background:

Yasmin is a combination oral contraceptive and contains a new molecular entity, drospirenone (DRSP), a progestin that has anti-mineralocorticoid activity similar to that of spironolactone.

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Draft Labeling
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1. Develop an educational outreach program for health care providers and patients, focusing on Yasmin®'s contraindications in patients with renal or hepatic impairment and in patients predisposed to hyperkalemia.
 - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports. Submit a final report within 6 months after completion of the program.
 - Include educational outreach for patients, which is not described in the November 6, 2000 proposal.
 - Educate healthcare providers to the importance of reporting all serious adverse events (especially cardiac events) that occur in Yasmin® users.
 - Provide healthcare providers with a mechanism to facilitate the reporting of serious adverse events in Yasmin® users.

2. Develop a surveillance program to a) evaluate the prescribing of Yasmin to contraindicated patients with underlying renal or hepatic impairment 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 renal and/or hepatic impairment. Submission of full case report summaries of all such contraindicated prescriptions, including patient outcome, would be required, and to b) evaluate compliance of healthcare providers with the serum potassium measurements in the first cycle of Yasmin® use in patients receiving long-term treatment with medications that may increase serum potassium
 - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.
 - Set acceptable limits approved by FDA for contraindicated prescribing of Yasmin® and describe the corrective actions that will be taken if the limits are exceeded.

3. Use a database to evaluate all patients prescribed Yasmin® for the subsequent outcomes 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.
 - Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives. Submit a final report within 6 months after completion of the program.
 - Ensure that the surveillance program based on the United Healthcare database will identify Yasmin® users who are hospitalized, receive emergency treatment, or who experience other serious adverse events.

4. Analyze more carefully pregnancy outcomes that occur in patients exposed to Yasmin®. This could be done in the same cohort of Yasmin® users described in the database described above. 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. Submit the final protocol to the FDA within 90 days of the approval date, initiate the program within 180 days of the approval date, and submit semi-annual status reports containing line listings, summary tables, and relevant subject narratives.
- the sponsor asked if supplying a phone number for providers to report Adverse Events (AE's) would be sufficient for meeting Phase 4 commitment number 1, 4th comment; the Agency responded that the provision of a telephone number would have to be accompanied by education to health care providers about reporting AEs
 - the Agency reminded the sponsor that there has been concern regarding the risk of hyperkalemia from this product throughout the Center, including senior management, and that concerns remain at a level such that if a problem is found with Yasmin, such as contraindicated patients being prescribed Yasmin having clinical problems, the sponsor will be called in to discuss further regulatory action needed to ensure safety with the product; it will be difficult for the Agency to support the product if such a situation should arise; appropriate marketing of this product was stressed by FDA and agreed to by the sponsor

Decisions:

- the action today is dependent on receipt of final draft labeling and acceptance of the Phase 4 commitments

Action Items:

- sponsor to submit final draft labeling within the hour
- sponsor to submit acceptance of the Phase 4 commitments within the hour
- J. Best to provide action letter by COB today
- Meeting minutes to sponsor within 30 days

Minutes Preparer

Concurrence, Chair

Note to Sponsor:

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best
HFD-580/Hixon/Monroe/Rumble
HFD-103/Houn
drafted: JAB/May 11, 2001
concurrence: Monroe, 05.11.01/Hixon, 05.11.01/Houn, 05.11.01
Final/JAB/May 11, 2001

MEETING MINUTES

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/s/

Florence Houn

5/11/01 05:33:07 PM

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Teleconference Meeting Minutes

Date: May 11, 2001

Time: 9:00-9:30 AM

Location: Parklawn; 13-B45

NDA 21-098

Drug: Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling

Meeting Chair: Dr. Florence Houn

External Lead: Ms. June Bray

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:

Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)

Dena Hixon, M.D., Clinical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Berlex Laboratories, Inc.

June Bray, Vice President, Drug Regulatory Affairs

Don Atkinson, Vice President, Female Healthcare

Sharon Brown, Director, Drug Regulatory Affairs

Marie Foegh, M.D., Medical Director, Clinical Research and Development, Female Healthcare

Jeff Frick, Strategic Business Director

Nancy Velez, Manager, Drug Regulatory Affairs

Meeting Objective: To discuss labeling recommendations provided by the Agency on May 10, 2001.

Background:

Yasmin is a combination oral contraceptive and contains a new molecular entity, drospirenone (DRSP), a progestin that has anti-mineralocorticoid activity similar to that of spironolactone.

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Draft Labeling
(not releasable)

Decisions:

- the sponsor's acceptance of the Agency's recommendations for labeling and Phase 4 plan will be the basis for approval of this product

Action Items:

- the sponsor will provide labeling revisions to the Agency later this morning
- The Agency will provide final Phase 4 program comments to sponsor by 12 Noon today
- Meeting Minutes to the sponsor within 30 days

Minutes Preparer

Concurrence, Chair

Note to Sponsor:

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

**APPEARS THIS WAY
ON ORIGINAL**

cc:

Original NDA

HFD-580/DivFile

HFD-580/Best

HFD-580/Hixon/Monroe/Rumble

HFD-103/Houn

drafted:JAB/May 11, 2001

concurrence:Hixon,05.11.01/Monroe,05.11.01/Houn,05.11.01

Final/JAB/May 11, 2001

MEETING MINUTES

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/s/

Florence Houn
5/11/01 05:44:14 PM

**APPEARS THIS WAY
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Teleconference Meeting Minutes

Date: May 9, 2001

Time: 2:00 – 2:45 PM

Location: Parklawn; 13-B45

NDA 21-098

Drug: Yasmin® 28 Tablets (drospirenone and ethinyl estradiol)

Indication: Oral Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Labeling

Meeting Chair: Dr. Florence Houn

External Lead: Ms. June Bray

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:

Florence Houn, M.D., M.P.H., Office Director, Office of Drug Evaluation III (ODE III; HFD-103)

Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manger, DRUDP (HFD-580)

External Attendees:

Berlex Laboratories, Inc.

June Bray, Vice President, Drug Regulatory Affairs

Don Atkinson, Vice President, Female Healthcare

Sharon Brown, Director, Drug Regulatory Affairs

Marie Foegh, M.D., Medical Director, Clinical Research and Development, Female Healthcare

Jeff Frick, Strategic Business Director

Nancy Konnerth, Manager, Advertising and Labeling

Loise Palma, Manager, Clinical Data Management, Clinical Operations

Harji Patel, Ph.D., Associate Director, Biostatistics

Paul Zhang, Senior Staff Statistician, female Healthcare

Nancy Velez, Manager, Drug Regulatory Affairs

Meeting Objective: To discuss labeling recommendations provided by the Agency on May 8, 2001.

Background:

Yasmin is a combination oral contraceptive and contains a new molecular entity, drospirenone (DRSP), a progestin that has anti-mineralocorticoid activity similar to that of spironolactone.

Discussion:

- there has been much discussion at the Division, Office and Center levels regarding the type of Action to be taken for this product, due to the risk/benefit profile; the label submitted to the sponsor on May 8, 2001 reflects the safety concerns of the Agency
- the Agency finds the sponsor's proposed risk management Phase 4 program to be favorable; the Agency does have comments that will be conveyed by Friday, May 11, 2001
- the Agency reported that the data submitted in the NDA indicates that Yasmin does lead to an increase in serum potassium, albeit a small increase as reported in the renal impairment, Ace inhibitor, and HRT studies, even though these studies were not designed to demonstrate serum potassium changes; therefore, the Agency remains concerned with this risk of hyperkalemia especially since there are numerous oral contraceptive products on the market that do not carry this risk, and the sponsor has not demonstrated a unique benefit with data presented in this application
- the sponsor disagrees with the Agency's concern regarding the potential for hyperkalemia with Yasmin use, especially in women who have conditions that predispose them for hyperkalemia or that take drugs that can lead to hyperkalemia; the sponsor specifically does not want a precaution for women that have a concomitant use of NSAIDS, or that have mild or moderate renal impairment; the Agency responded that the sponsor can propose wording for NSAID use such as "long-term daily use of NSAIDS", but that precaution in concomitant use of Yasmin with NSAIDS would remain in the label because the studies were not designed to specifically address this issue; the Agency also does not agree with dropping the precaution of use of Yasmin in women with mild or moderate renal impairment because the study done by the sponsor to address this issue was a very small study with a controlled diet that limited potassium exposure; also, the sponsor presented data showing that only a small number of women of contraceptive age have renal impairment
- the sponsor disagreed with the precaution of checking a serum potassium level during the first month of Yasmin use if women are on concomitant medications that can lead to hyperkalemia; the Agency responded that that a similar statement is in the European labeling and that the sponsor has not presented data in their NDA to alleviate the concerns regarding the potential for hyperkalemia; substantial safety data from future post-marketing information can lead to a less restrictive label; the sponsor stated that they thought it would be impossible to market their product if they had restrictions that were not present in other oral contraceptive labels
- the sponsor disagreed with the **Bolded Warning** in the Brief Summary Patient Package Insert; the sponsor stated that this warning would lead to women electing not to use Yasmin, and that they had performed market research on how to explain the use of drospirenone to potential users of Yasmin, and would prefer a reference to drospirenone with its diuretic properties rather than its potential for hyperkalemia properties; the Agency responded that the goal of patient labeling is to inform the patient of risks with a drug product; the Agency also responded that referring to drospirenone as a diuretic would imply an unintended, unproven claim and would not be acceptable; the sponsor may propose alternate wording to the Agency for review
- the sponsor also reported that the marketing of Yasmin in Europe is going well and that no cases of hyperkalemia have been reported to date; the Agency responded that a submission of a summary of all post-marketing data would be helpful

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Decisions:

- the sponsor's acceptance of the Agency's recommendations for labeling and Phase 4 plan will be the basis for approval of this product; if disagreement remains on Friday, May 11, 2001, then additional time will be needed for discussion and an approvable action will be likely to allow for the extra discussion and agreement

Action Items:

- the sponsor will provide labeling revisions to the Agency by COB today, May 9, 2001
- The Agency will provide final Phase 4 program comments to sponsor by Friday, May 11, 2001
- Meeting Minutes to the sponsor within 30 days

Minutes Preparer

Concurrence, Chair

Note to Sponsor:

These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

**APPEARS THIS WAY
ON ORIGINAL**

cc:

Original NDA

HFD-580/DivFile

HFD-580/Best

HFD-580/Monroe/Rumble

HFD-103/Houn

drafted: JAB/May 9, 2001
concurrency: Monroe, 05.09.01/Rumble, 05.09.01/Houn, 05.10.01
Final/JAB/May 10, 2001

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
5/10/01 01:56:05 PM
CSO

Florence Houn
5/11/01 04:29:28 PM
UNKNOWN

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ON ORIGINAL**

TELEFAX
UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

February 2, 2000

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

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



ORIG AMENDMENT

Dear Dr. Allen:

BM

Re: **NDA 21-098 – YASMIN® 21/28 TABLETS**
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Miscellaneous Clinical Review Questions

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 telephone conversations between Ms. Jeanine Best of the Division and the undersigned on December 9th, 1999, and January 3rd and 18th, 2000 during which Ms. Best communicated miscellaneous questions from the Medical Reviewer on our NDA. Answers to these questions are provided below.

Subject with Increased Liver Enzymes (US Report 98180)

On December 9th, Ms. Best informed the undersigned that the Medical Reviewer is concerned about Subject 4902027 in the US study 96049B (Report 98180). She stated that this is a 23 year old subject with normal baseline values who at Cycle 6 had increased liver enzymes. The reviewer asked for any repeat labs or follow up information that may indicate possible causes.

REVIEWS COMPLETED	
COORDINATOR	
<input type="checkbox"/> LETTER	<input type="checkbox"/> FAX
COORDINATOR	DATE

We have reviewed the Case Report Form of Subject 4902027 and provide the following information:

Lab Parameter	Screening Labs 1/28/1997	Visit 6 07/22/1997	Final Visit 13 2/24/1997
	53	37	54
	12	16	36
	23	21	91

The investigator made an assessment during the final visit that these values were not clinically significant. No additional follow-up labs were done.

Clarification of Number of Subjects (US Report 98180)

On January 3rd, Ms. Best referred the undersigned to US Report 98180, NDA Vol. 147, page 8 38977. The Medical Reviewer questioned the subject numbers cited in the following paragraph:

A total of 231 (71%) of the 326 subjects who were evaluated, completed 13 treatment cycles and the required follow-up visit at 3 months. All 13 treatment cycles were completed by 220 subjects (68%). Regardless of completing the study, 237 subjects (73%) of the 326 evaluated subjects had a 2-week follow-up visit. The majority of subjects ($\geq 55\%$) from each study center completed all 13 cycles of treatment.

The Medical Reviewer asked whether the number of subjects with a 2 week follow-up visit (237) were reversed with the number of subjects who completed the 13 cycles and the 3 month follow-up visit (231).

We have reviewed the numbers cited in the above paragraph and conclude that they accurately reflect the results of the study.

This information was also provided verbally to Ms. Best by the undersigned in a voice mail communication on January 20th and in a conversation with Ms. Sharon Brown of Berlex on January 24th.

Pregnancies and Adverse Events (AE) in Foreign Report AI51

On January 18th, Ms. Best asked the following questions with regard to Foreign Report AI51:

1. For pregnancies occurring in the study, the Medical Reviewer wanted to know how the gestational age was determined. She asked how we knew that the subjects weren't pregnant during the study, not that they got pregnant after the study medication was stopped? Ms. Best provided the following subject numbers: 9, 104, 290, 462, 645, 677, and 715.
2. The Medical Reviewer asked for additional information regarding Subject 255 who experienced thrombophlebitis.

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3. The Medical Reviewer asked for additional information regarding Subjects 103, 364, 112, and 155¹ who experienced peripheral vascular disorder as an AE.

A table providing detailed responses to all three of the above questions is attached.

We trust that the information provided in this submission addresses all of your concerns and will enable you to complete the review of the NDA. 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/drproc024

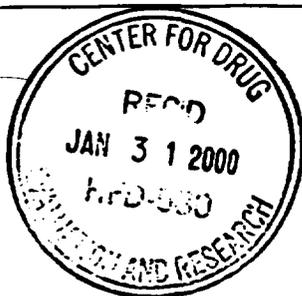
Desk copy (cover letter): Ms. Jeanine Best

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¹ Upon researching, it was determined that the subject number must have been 151 rather than 155.



January 28, 2000



Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

ORIG AMENDMENT

BC

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

REVIEWS COMPLETED
CSO INITIALS
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
DATE

Dear Dr. Allen:

**Re: NDA 21-098 – YASMIN® 21/28 TABLETS
(Drospirenone 3 mg and Ethinyl Estradiol 0.030 mg Tablets)
OTHER: Response to Chemistry Information Request Letter of
December 16, 1999**

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 your letter of December 16, 1999 which contained comments and information requests which resulted during the review of the Chemistry section of our NDA.

This submission provides responses to the comments in your letter of December 16th. (A copy of the December 16th letter immediately follows this cover letter for your reference.) The Division's comments are provided first in bold, followed by our responses.

- 1. Please provide certificates of analysis of the drug substance batches (#'s 80301, 80302, and 80303) that were used in the manufacture of drug product batches SH T 470 FA.**

The following table presents an overview on the ethinyl estradiol and drospirenone drug substance batches used in the manufacture of drug product batches 80301, 80302 and 80303.

Certificates of Analysis are provided respectively in Attachment 1.

DP batch	Drug substances	Batch no.	Certificate no.
80301	DRSP EE	47052334 47052300	97014670 98000908
80302	DRSP EE	47052335 47052300	97014671 98000908
80303	DRSP EE	47052336 47052300	97014669 98000908

EE = Ethinyl estradiol
DRSP = Drospironone

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.

Release testing of drug substance batches is performed at Schering AG, Berlin. Upon receipt at Schering Production Company, Weimar, drug substance batches are confirmatory tested for identity only. Identity is checked by IR spectroscopy according to the Schering Testing Standards valid at that time.

3. Please provide the name and address of the facility used for acceptance (confirmatory) testing of raw materials, including drug substances and excipients.

Confirmatory testing of raw materials, drug substances and excipients is performed at:

Schering GmbH und Co. Produktions KG (Schering Production Company)
Doebereinerstrasse 20
99427 Weimar
Germany

4. When the desired weight of 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 confirmatory assay test performed on the batch at the drug product manufacturing site.

Analytical results as given in respective Certificates of Analysis are used for calculating ACP (assay calculation purposes).

EE: ACP = $ADB \times (100 - LD) / 100$
 ADB = assay in %, calculated on the dried basis
 LD = loss on drying in %

DRSP: ACP = $ADB \times (100 - (S1+S2+W)) / 100$
 ADB = assay in %, calculated on the dried basis
 S1 = dimethoxyethane in %
 S2 = diisopropylether in %
 W = water in %

When calculating an ACP for values greater than 100.0 %, an ADB of 100.0 % is used.

5. Please provide information on the compatibility between _____ (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.

YASMIN tablets T 470 FA are immediately packed into _____ bags after being manufactured at the Weimar production plant. Bag material used for storage of bulk tablets is:

Compatibility between the _____ bags and the YASMIN tablets are derived from investigations on bulk stability. In order to fulfill the requirement of the Guidance for Industry Container Closure Systems for Packaging Human Drug and Biologics, May 1999, Section VI.B, bulk tablets have been investigated after storage at 25 °C/60% r.h. (12 months) and at 40 °C/75% r.h. (6 months). No differences in degradation behavior compared to blister storage have been observed, therefore compatibility is considered to be proven. Detailed information is provided in:

- Stability Report No. QE2-026.4/98
Stability Report on SH T 470 FA (shipping container), including annex dated January 4, 2000 (see Attachment 2).

Tests on chemical purity and appearance are performed according to USP and 21 CFR § 177.1520 olefin polymers and is provided in:

- Testing Standard No. 1045
dated June 16, 1999 (see Attachment 3).

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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.

Prior to the film-coating process, tablet cores are stored at the production site in stainless steel containers (tight containers). Humidity and temperature are controlled for the following conditions:

Temperature requirement:
20 °C, permissible range: _____

Humidity requirement:
50 % r.h., permissible range: _____

Deviation from the ranges causes alert.

Tablet cores must be processed within 4 weeks. In case of exceeding the permissible storage time, the Head of Production and the Head of Quality Control decide on further actions to be taken.

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.

YASMIN Tablets, manufactured at the production plant in Weimar are packed into bags and stored under controlled conditions until the transfer to the packaging unit in Berlin is performed. Bulk YASMIN Tablets thereafter are stored at the Berlin warehouse until blister packaging is initiated.

Weimar production plant:

Temperature requirement: 18 °C, permissible range: _____

Humidity requirement: 40 % r.h., permissible range: _____

Storehouse Berlin:

Temperature requirement: 20 °C, permissible range: _____

Humidity requirement: 50 % r.h., permissible range: _____

- exception during Christmas holidays, _____

Given stability has been proven, the time period covered by stability testing of the bulk tablets (which in case of YASMIN Tablets is 12 months) is considered to be the maximum time between manufacturing of the coated tablets and blister packaging.

- 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).**

Diagrams schematically describing the complete YASMIN packaging process are provided in Attachment 4.

- 9. Please provide release specifications that include testing for impurities and degradation products.**

The release specifications include testing for impurities and decomposition products (see revised Quality Specification No. K280E280 provided in Attachment 5 in response to Comment 10).

Furthermore it was proven that during the development of YASMIN Tablets the pharmaceutical manufacturing process does not lead to any decomposition of both drug substances. Therefore, Schering AG intends to omit testing for decomposition products in the drug product release specification.

- 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%.**

Considering ICH Q3B and reflecting the recent 18-month stability results of YASMIN Tablets (see response to Comment 16 and Attachment 8), Schering AG herewith agrees to lower the specification for any unidentified decomposition product to 0.3%.

As the maximum daily intake of drospirenone is 3 mg, the proposed specification limit corresponds to a total daily intake (TDI) of 9 µg. According to ICH Q3B, a daily intake in the range of 1 – 10 mg would require a specification limit of 0.5%. Therefore, the even tighter limit for any unidentified decomposition product of drospirenone is considered to be justified and in line with the requirements of ICH Q3B.

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The revised specification:

- **Quality Specification No. K280E280**
Yasmin-30, film-coated tablet
dated Jan 17, 2000

is provided in Attachment 5 and also covers adjustments on:

- limit of the iso-compound (0.1 %)
- total of decomposition products of drospirenone (0.5 %)
- content of drospirenone / _____
- and
- dissolution of ethinyl estradiol and drospirenone _____

11. Please tighten the limit for the iso-compound and the total impurities of drospirenone to reflect the available stability results.

Upon review of the recent 18-month stability results of YASMIN Tablets (see response to Comment 16 and Attachment 8), Schering AG herewith agrees to tighten the specification for the iso-compound to 0.1% and for total impurities of drospirenone to 0.5%.

The adjusted specification (see Attachment 5):

- **Quality Specification No. K280E280**
Yasmin-30, film-coated tablet
dated Jan 17, 2000

also includes additional adjustments (as requested in Comment 10).

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.

Schering AG herewith agrees to tighten the specifications on "Absence of ethinyl estradiol" and "Absence of drospirenone" according to the proposed limits.

Ethinyl estradiol: $\leq 0.5 \%$ (corresponding to $\leq 0.15 \mu\text{g}/\text{tablet}$ and the limit of detection of $0.15 \mu\text{g} / \text{tablet}$)

Drospirenone: $\leq 0.01 \%$ (corresponding to $\leq 0.2 \mu\text{g}/\text{tablet}$ and the limit of detection of $0.2 \mu\text{g} / \text{tablet}$)

The revised specification:

- Quality Specification No. LL00E230
SH T 470 PD, Placebo film-coated tablet
dated Jan 17, 2000

is provided in Attachment 6.

13. Regarding the dissolution testing of ethinyl estradiol and drospirenone by HPLC, it is stated on page 4:4:682 that linearity is validated for _____ for ethinyl estradiol and _____ for drospirenone. It is also stated that these ranges correspond to _____ for ethinyl estradiol and _____ for drospirenone when accounting for the 900 mL dissolution medium. However, results on pages 4:4:693-4:4:696 show linearity is validated for _____ for ethinyl estradiol and _____ for drospirenone. Please comment on the discrepancy.

By mistake the amounts of both ethinyl estradiol and drospirenone have been presented in incorrect mass units, µg instead of ng (correct mass unit). Linearity is validated for _____ ng for ethinyl estradiol corresponding to _____ and for _____ ng for drospirenone corresponding to _____

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.

Schering AG confirms that information on the operating temperature of the applied HPLC method has not been given on page 4:4:715 of the Working Report QP2/029/90. However, the requested information is routinely included in the Testing Standard valid at the time of investigation. Please therefore also see page 24 of the revised Testing Standard No.K280E160, dated Jan 17, 2000, which is provided in Attachment 7.

Operating temperature:

Schering AG confirms that the peak assignment for the chromatograms 5-6 on page 4:4.718 of the Working Report QP2/029/090 is not given. The assignment can be derived from the table

given in the report.

Peak assignment chromatogram 5:

min internal standard
min drospirenone

Peak assignment chromatogram 6:

min ethinyl estradiol
min internal standard

Validation of the degradation products of drospirenone has been limited for selectivity and determination of the limit of detection of drospirenone. Although the requirements defined in the ICH Validation Guideline request a more extended validation, Schering AG justifies the restricted validation approach for the following reasons:

1. Long-term and accelerated stability studies of the drug product according to ICH conditions (25°C/60% r.h., 30°C/70 % r.h. and 40°C/75 % r.h.) reveal that the iso-compound, the only degradation product of DRSP to be expected, has never been determined, being similar to below 0.01 %. Any other decomposition products are at or below the limit of detection (Stability Report No. QE2-025.4/98, see Attachment 8).
2. The photostability test on YASMIN tablets has shown that no decomposition of drospirenone occurs (Working Report QE2-016.1/98, NDA Vol. 4, page 4 - 558).
3. Despite the fact that neither the drospirenone drug substance nor the drug product show decomposition, the very low detection limit would also assure detection of any potential decomposition products. The selectivity of the method was shown for several compounds (Working Report QP2/029/90):

The validation of the test method is therefore considered to be sufficient to assure detection of any decomposition product.

4.

15. Please provide a validation report regarding the HPLC test method for absence of ethinyl estradiol and drospirenone.

Determination of ethinyl estradiol and drospirenone in placebo tablets is performed applying the same HPLC method as for assay testing in YASMIN Tablets. Therefore, no separate validation report is provided, but reference is given to:

- Working Report No. QP2/029/90
Validation on the HPLC determination of assay and the dissolution of dihydrodrospirenone and ethinylestradiol in SH T 470 (E,F,I and K) film-coated tablets dated Dec 20, 1990
(NDA Vol. 4, page 4 – 713)

16. Please provide the complete 12-month stability data, a proposed shelf-life for Yasmin™ Tablets, and a post-approval stability protocol.

Stability testing on YASMIN Tablets started on May 28, 1998. At the time of the initial NDA submission, and as agreed during the Phase 3 meeting of February 12, 1997 between Berlex and the Division, only 6 months data were presented in the NDA. Berlex committed to amend the NDA with 12-month stability data during the NDA review. On January 7, 2000, Berlex submitted 12 month stability data (Stability Report No. QE2-025.3/98).

Recently, 18-month data on the same three production scale batches included in the 12-month report and manufactured in Weimar, Germany have become available.

The extended stability data are provided in Attachment 8:

- Stability Report No. QE2-025.4/98
Stability Report on SH T 470 FA (with pouch)
dated Jan 13, 2000

Over the entire storage period, YASMIN™ Tablets remain well within the limits, briefly described by general tendencies as:

Appearance, microbial contamination and the content of drospirenone remain unaffected by storage for 18 months at 25 °C/60 % r.h., 30 °C/70 % r.h. and 30 °C/35 % r.h. and after a 6 month storage at 40 °C/75 % r.h.

While dissolution on drospirenone remains unaffected over the entire time period and under all conditions, an average decrease of around 10% in dissolution of ethinyl estradiol is seen.

The total amount of decomposition products of drospirenone remain unaffected at the very low level of n.d. (=0.01%) to 0.03%, corresponding to the unchanged assay values. The well known time and temperature dependent increase of ethinyl estradiol decomposition products – significant at 40 °C/75 % r.h (0.32 – 2.12% at maximum) - is

confirmed in YASMIN™ Tablets also, but is somehow overcompensated (well known for other products containing ethinyl estradiol) by the decrease in content values (1 - 5%).

For in-depth evaluation of stability results reference is given to the above-mentioned report.

To support the above mentioned results, 24-month data on three pilot scale batches are also presented in Attachment 9:

- Stability Report No. QE2-020.3/97
Stability Report on SH T 470 FA (with pouch)
dated June 7, 1999.

Based on the most recent results provided in the 18-month stability report, the following shelf life for YASMIN Tablets is proposed:

_____ stored up to 25 °C.

Please note that a post approval stability protocol was included with the 12-month stability data in our submission of January 7, 2000.

17. Please revise the pouch and carton labels to read: "drospirenone and ethinyl estradiol . _____"

Due to a 3 month lead time for printing _____ we have already printed enough _____ or launch, therefore, we are requesting that we be allowed to revise the pouch stock for six months or until supply has been depleted, whichever comes first.

The carton labeling has been revised accordingly.

18. Please revise the storage statement on the carton 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 units in this carton contains two pieces of information . . ."

"Manufactured for Berlex Laboratories, Wayne, NJ 07470 by Schering GmbH, Germany".

With regard to the first two comments we have revised the cartons accordingly. With regard to the inclusion of "by Schering GmbH", according to 21 CFR 201.1(g), which states in part that "[t]he requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporate person, only by the actual corporate name, except that the corporate name may be that of a parent, subsidiary, or affiliate company, where

the related companies are under common ownership and control." Under this regulation, the Berlex name can be used in place of the Schering name, as Schering and Berlex are parent and subsidiary, respectively.

Therefore, we propose the following language:

Manufactured for Berlex Laboratories

Wayne, NJ 07470

Manufactured in Germany

This language is consistent with all other products marketed by Berlex and manufactured in 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 by Schering GmbH, Germany".

With regard to the storage temperature, the blister has been revised accordingly.

We did not include a storage statement on the pouch because it appears on the blister and carton. The patient does not keep the foil, it is discarded once it is opened. Due to a 3 month lead time for printing foil, we have already printed enough foil for launch, therefore, we are requesting that we be allowed to use the already printed pouch stock for six months or until supply has been depleted, whichever comes first. We will then revise the pouch accordingly.

As previously stated, with regard to the inclusion of "by Schering GmbH", according to 21 CFR 201.1(g), which states in part that "[t]he requirement for declaration of the name of the manufacturer, packer, or distributor shall be deemed to be satisfied, in the case of a corporate person, only by the actual corporate name, except that the corporate name may be that of a parent, subsidiary, or affiliate company, where the related companies are under common ownership and control." Under this regulation, the Berlex name can be used in place of the Schering name, as Schering and Berlex are parent and subsidiary, respectively.

Therefore, we propose the following language:

Manufactured for Berlex Laboratories

Wayne, NJ 07470

Manufactured in Germany

As stated previously, this language is consistent with all other products marketed by Berlex and manufactured in Germany.

20. Each carton contains three units (boxes/cartons), each constituting of the brief and detailed patient package insert, 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.

The single unit carton is identical to the outer carton except with regard to the # of units and the NDC number. The label for the single unit carton for YASMIN 21 and 28 TABLETS is provided in Attachment 10.

We trust that the information provided in this submission addresses all of your concerns and will enable you to complete the review of the NDA. 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/drpac010

Desk copy (cover letter): Ms. Jeanine Best

**APPEARS THIS WAY
ON ORIGINAL**