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/s/

Scott Dallas
8/15/03 10:39:54 AM
PHARMACIST

Denise Toyer
8/15/03 10:42:51 AM
PHARMACIST

Carol Holquist
8/15/03 10:56:29 AM
PHARMACIST

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: Karen Anderson
Project Manager
HFD-580

Date: May 20, 2003

Re: ODS Consult 01-0240-2; Seasonale (Levonorgestrel and Ethinyl Estradiol Tablets) 0.15 mg/0.03 mg; NDA 21-544.

In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), DMETS reviewed the proposed blister label and carton labeling of Seasonale, for possible interventions that may help minimize medication errors.

The proprietary name, Seasonale, was originally reviewed on September 10, 2002 (see ODS consult 01-0240) and re-reviewed on March 29, 2003 (see ODS consult 01-0240-1). In both instances, DMETS had no objections to the use of the name.

In reviewing the blister label and carton labeling for Seasonale, DMETS identified a couple areas of possible improvement in minimizing the potential for medication errors.

General Comments

1. DMETS questions the use of the statement ' [redacted] on carton labeling. DMETS has concerns that [redacted] will be used to advertise this product in which case physicians may write for [redacted] rather than "Seasonale." This may cause confusion among pharmacists as they may be familiar with the proprietary name "Seasonale" and not the term [redacted]

2. Remove the [redacted] from the established name and revise on all labels and labeling to read:

   (levonorgestrel and ethinyl estradiol tablets, USP)
   0.15mg/0.03 mg

   Additionally, ensure that the established name is at least 1/2 the size of the proprietary name.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Alina Mahmud
5/21/03 03:06:55 PM
PHARMACIST

Carol Holquist
5/22/03 06:44:17 AM
PHARMACIST

Jerry Phillips
5/22/03 08:41:26 AM
DIRECTOR

Office of Drug Safety

Memo

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

CC: Karen Anderson
Project Manger
HFD-580

Date: March 29, 2003

Re: ODS Consult 01-0240-1; Seasonale (Levonorgestrel/Ethinyl Estradiol Tablets) 150 mcg/30 mcg; NDA # 21-544

This memorandum is in response to a March 10, 2003, request from your Division for a re-review of the proprietary name, Seasonale.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Seasonale since we conducted our initial review on September 10, 2002 (ODS consult # 01-0240) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Tia Harper-Velazquez
3/24/03 10:13:28 AM
PHARMACIST

Alina Mahmud
3/24/03 10:30:22 AM
PHARMACIST

Carol Holquist
3/24/03 01:03:32 PM
PHARMACIST

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 12/14/01	DUE DATE: 9/25/02	ODS CONSULT #: 01-0240

TO:

Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Jennifer Mercier
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Barr Laboratories, Inc.
Seasonale (Levonorgestrel and Ethinyl Estradiol Tablets) 150 mcg/30 mcg NDA #: 21-544 (IND # 60,399)	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Seasonale" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS has no objection to the use of the proprietary name, "Seasonale"; however, DDMAC [redacted] see section II of review). In addition, DMETS recommends the sponsor implement an education campaign that will inform practitioners of the difference in the packaging configuration as well as the correct dosage and administration. DMETS also recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 10, 2002

NDA NUMBER: 21-544

NAME OF DRUG: Seasonale (Levonorgestrel and Ethinyl Estradiol Tablets) 150 mcg/30 mcg

NDA HOLDER: Barr Laboratories, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename "Seasonale", regarding potential name confusion with other proprietary/established drug names. The sponsor also submitted a Trademark Research Report that was conducted by Thomson & Thomson to help in DMETS' search for sound-alike and look-alike names.

PRODUCT INFORMATION

"Seasonale" is a combination oral contraceptive drug product containing 30 mcg of ethinyl estradiol as the estrogenic compound and 150 mcg of levonorgestrel as the progestational compound. It is indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception. "Seasonale" will be supplied as a 91-day regimen where patients take one active tablet per day for 84 days followed by one inactive tablet per day for 7 days. During the first cycle of medication, the patient should take "Seasonale" on the first Sunday after the onset of menstruation. The patient should then begin her next and all subsequent 91-day courses of tablets on the same day of the week (Sunday) on which she began her first course, following the same schedule (84 days of active tablets and 7 days of inert tablets).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Seasonale" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's

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[1] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov.

SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Seasonale". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. There were minor concerns with *Seconal,* which is listed in Table 1 (see below) along with the dosage forms available and usual dosage.

2. DDMAC had concerns [redacted]

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Seasonale	Levonorgestrel and Ethinyl Estradiol (Rx) Tablet: 150 mcg/30 mcg	1 tablet once a day.	
Seconal	Secobarbital Sodium (Rx) Capsule: 100 mg	Preoperative Sedation 200 mg to 300 mg 1 to 2 hours before surgery. Bedtime Hypnotic 100 mg at bedtime.	*SA

*Frequently used, not all-inclusive.
**SA (sound-alike), LA (look-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Seasonale" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a

[5] WWW location http://www.thomson-thomson.com.

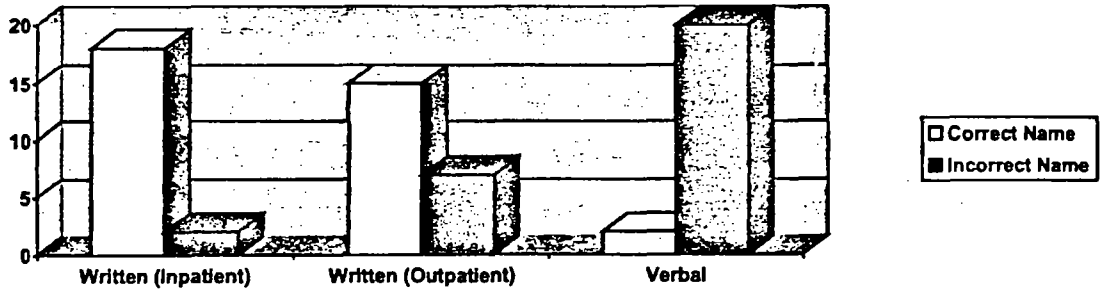
prescription for "Seasonale" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: Virginia, Seasonale daily as directed	*Outpatient Rx:* Seasonale. Use as directed. Number one.
Outpatient Rx: Seasonale ad dir #1	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Seasonale"	Incorrectly Interpreted
Written Inpatient	35	20 (57%)	18 (90%)	2 (10%)
Written Outpatient	32	22 (69%)	15 (68%)	7 (32%)
Verbal: Outpatient	39	22 (56%)	2 (9%)	20 (91%)
Total	106	64 (60%)	35 (55%)	29 (45%)



Among the written inpatient prescriptions, 2 (10%) out of 20 respondents interpreted "Seasonale" incorrectly. Incorrect interpretations included *Secesonale* (1 respondent, 5%) and *Seavonale* (1 respondent, 5%).

Among the written outpatient prescriptions, 7 (32%) out of 22 respondents interpreted "Seasonale" incorrectly. Incorrect interpretations included *Seascuale* (4 respondents, 18%), *Scascuale* (2 respondents, 9%), and *Seascnale* (1 respondent, 5%).

Among the verbal outpatient prescriptions, 20 (91%) out of 22 respondents interpreted "Seasonale" incorrectly. Incorrect interpretations included *Seasonal* (10 respondents, 45%), *Seconal* (2 respondents, 9%), *Suthenal* (1 respondent, 5%), *Cefenal* (1 respondent, 5%), *Cefonal* (1 respondent, 5%), *Cesenow* (1 respondent, 5%), *Semptrol* (1 respondent, 5%), *Seasonelle* (1 respondent, 5%), *Sesonal* (1 respondent, 5%), and *Seasonall* (1 respondent, 5%).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Seasonale", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such concerns included *Seconal*.

Seconal is the proprietary name for secobarbital sodium, a CII drug product, and is indicated as a preanesthetic and a hypnotic (for the short-term treatment of insomnia since it appears to lose its effectiveness after 2 weeks). The recommended dosage for preoperative sedation is 200 mg to 300 mg 1 to 2 hours before surgery and 100 mg for use as a bedtime hypnotic. *Seconal* is available as a 100 mg capsule. *Seconal* sounds similar to "Seasonale". The "Se" in *Seconal* is pronounced the same as "Sea" in "Seasonale" and the "onal" in *Seconal* may sound identical to "onale" in "Seasonale" as demonstrated in the DMETS study where 19 respondents' (86%) interpretation of "Seasonale" did not include the terminal "e". Of those 19 respondents, 10 (45% out of 22 respondents) interpreted "Seasonale" as *Seasonal*. More significantly, two respondents (9%) interpreted "Seasonale" as *Seconal*. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretations with these drug products. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Also, both are available in one strength, are given once a day, and can be dispensed in retail pharmacies ("Seasonale" would typically not be dispensed in hospital pharmacies). However, the main concern of confusion between *Seconal* and "Seasonale" is the verbal ordering of these drug products. *Seconal* is a CII drug product where prescriptions for *Seconal* cannot be taken over the telephone in a retail pharmacy, but must be ordered through written prescriptions. Thus, this decreases the potential risk of medication errors through verbal communication between *Seconal* and "Seasonale". As a written prescription, *Seconal* and "Seasonale" do not look similar.

The [redacted] submitted by the sponsor did not yield any significant sound-alike or look-alike names.

DDMAC does have concerns [redacted]

In regards to the packaging configuration, traditionally, birth control pills are available in packages of 21 or 28 tablets (one month supply). This is different from the packaging configuration of "Seasonale", which is available as a three month supply (91 tablets). Some practitioners may not realize that one pack of "Seasonale" is a three month supply of tablets. If a prescriber writes a prescription for "Seasonale, 3 month supply, use as directed", a pharmacist who is not familiar with the drug product may dispense three packs of "Seasonale" instead of one, mistakenly believing that one pack is a one month supply instead of a three month supply. Therefore, DMETS recommends the sponsor implement an education campaign that will inform

practitioners of the difference in the packaging configuration as well as the correct dosage and administration.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CARTON LABELING (Carton and Pouch)

A highlighted statement such as ' [redacted] ' should appear on the main panel of the carton label and pouch .

B. INSERT LABELING (Package Insert and Patient Information Insert)

Patient Information Insert

1. The [redacted] subsection that is under the [redacted] section contain [redacted] This subsection should be clarified.

2. Under the IF YOU MISS 3 OR MORE PINK "ACTIVE" PILLS IN A ROW section, the first sentence may seem confusing to patients. The first sentence may be revised, for example, to state " [redacted]

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name "Seasonale"; however, DDMAC has concerns that the name "Seasonale" could appear misleading.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

B. [redacted]

C. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Jennifer Fan
9/24/02 10:38:12 AM
PHARMACIST

Denise Toyer
9/24/02 03:55:53 PM
PHARMACIST

Carol Holquist
9/24/02 03:59:35 PM
PHARMACIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
ıil: ODS (Room 15B-08, PKLN Bldg.)

FROM: Karen Anderson, N.P. – Project Manager
Division of Reproductive & Urologic Drug Products
(HFD-580)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 5, 2003		18-782 & 18-668		

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nordette 21 & 28	Standard	Oral Contraceptive	May 5, 2003

NAME OF FIRM: WYETH

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- X ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW)THER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- X CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
We would like AERS safety database information on the Nordette OC.
Please focus on Thromboembolic complications. It is requested in relationship to a new OC with the same active formulation (Seasonale).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
IATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Karen Anderson

4/4/03 09:17:11 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Marketing, Advertising and Communications (DDMAC)
12; Parklawn Bldg. Room 17B-17
Attention: Lisa Stockbridge

FROM:
Karen Anderson, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580
301-827-4259

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 8, 2003		21-544	labeling	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Seasonale (Levonorgestrel/EE) tablets		Oral Contraceptive	May 5, 2003

NAME OF FIRM: Barr Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

This NDA has a goal date of June 5, 2003. This OC has a different dosing regimen than previous products. It is to be used 84 / 7 meaning the active ingredient tablets are taken daily for 84 days followed by 7 days of inactive ingredient placebo tablets. Review material will be hand-carried to DDMAC.

Thank you.

URE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

3 Page(s) Withheld

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/s/

Lisa Stockbridge
5/5/03 01:10:59 PM
DDMAC REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 9/5/03

To: Christine Mundkur	**From:** Karen Anderson, NP
BARR	Division of Reproductive and Urologic Drug Products
Fax number: (201) 930-3318	**Fax number:** (301) 827- 4267
Phone number: (201) 930-3600	**Phone number:** (301) 827- 4259

Subject: Approval letter for Seasonale NDA 21-544

Total no. of pages including cover: 48

Comments:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 8/27/03

To: Christine Mundkur	**From:** Karen Anderson, NP
BARR LABS.	Division of Reproductive and Urologic Drug Products
Fax number: (201)930-3318	**Fax number:** (301) 827- 4267
Phone number:	**Phone number:** (301) 827- 4259

Subject: Request for information

Total no. of pages including cover: 2

Comments:

NDA 21-544 Seasonale
REQUEST FOR:

CARTON LABELING –We will need final carton labeling to include the descriptor that will replace [redacted]

We will also expect final printed labeling for the Package Insert and Patient Information sheet.
Also, please include the figure(s) of the pill cards.

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FAX

DATE: 14-OCT-2002

To: Sharif Ahmed	**From:** Su Tran, Ph.D. Chemist
Company: Barr Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 845-353-3859	**Phone number:** 301-827-4260
Phone number: 845-353-8432 ext. 0	

Subject: NDA 21-544

Total no. of pages including cover: 3

Comments:
Attached please find the meeting minutes for our phone call today.

Document to be mailed: ☐ YES ☑ NO

Teleconference Minutes

Date: October 14, 2002

NDA 21-544 , **Drug:** Seasonale
Applicant: Barr Laboratories, Inc.

Meeting Chair:	Su Tran, Chemist
Type of Meeting:	Chemistry (Guidance)
External Participant Lead:	Sharif Ahmed

Meeting objective: Request from FDA for additional CMC data.

Background:

- The drug product Seasonale is the same as the marketed Portia, which was approved by the Office of Generic Drug on 23-MAY-2002 under ANDA 75-866.
- The approved Portia is packaged for a 28-day regimen (one blister card with 28 tablets), while the NDA product Seasonale is packaged for a 91-day regimen (two blisters cards each with 28 tablets and one blister card with 35 tablets).
- Stability data are provided in the NDA for three batches of Portia to support the expiry of Seasonale.
- The product-contact components of the primary packaging are the same for both products.
- The main issue is that the dimensions of the blister cards are different for Portia and Seasonale, with the space between cavities and card edges being the most critical difference. In the amendment dated 31-OCT-2002, it is stated that the [redacted] for each of the Seasonale blister cards. In addition, the 35-tablet Seasonale blister card [redacted] while the Portia blister card has this

Discussion:

- FDA acknowledges that the risk of interactions between the product-contact components of the packaging and the tablets is small. In addition, the product-contact components are the same for Seasonale and the approved Portia.
- However, the dimensions of the blister cards are different for Portia and Seasonale, with the space between cavities and card edges being the most critical difference, and FDA is concerned about moisture permeation being a potential problem for the stability of the drug product. Since stability data for Portia are being used to support an expiry for Seasonale, additional data are required in order to show the equivalence of sealing integrity between the blister card of Portia and the blister cards of Seasonale.
  - An equivalence study should be performed per USP 25 <671> Containers-Permeation (Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets Method II specifically for blisters) and for no less than 28 days under conditions described in the USP method. Comparative results should be submitted for the Portia blister card and the three blister cards of Seasonale.

- The applicant stated that the testing per USP <671> has been ongoing, with at least four test time points during the 28-day testing period. Data will be available for submission in the next few weeks.

Decisions made: The additional data requested by FDA will be submitted in an amendment in the next few weeks.

Action items: Meeting minutes will be faxed to the applicant within 48 hours.

Note to applicant: 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.

/S/

Su Tran, Ph.D., Review Chemist
HFD-580
Phone (301) 827-4260

Cc: NDA 21-544
HFD-580/Division Files

Created by: STran
Finalized: STran

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

/s/

Suong Tran
11/14/02 02:59:51 PM
CHEMIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
A 21-544	Efficacy Supplement Type SE-	Supplement Number	
Drug: SEASONALE		Applicant: BARR LABORATORIES	
RPM: Karen M. Anderson, N.P.		HFD-580	Phone # (301) 827-4260
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 5, 2003 / Sept. 5, 2003
❖ Special programs (*indicate* all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted **21 CFR 314.53 "Method of Use"**	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	Aug. 28, 2003
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	NA

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AM - Clinical data May 30, 2003
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release (X) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	Sept. 4 and 5, 2003
• Original applicant-proposed labeling	July 23, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Aug. 27, 2003
• Documentation of discussions and/or agreements relating to post-marketing commitments	T-Con Aug. 27, 2003
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	Filing
❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Sept. 5, 2003
❖ Clinical review(s) *(indicate date for each review)*	Sept. 4, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Sept. 4, 2003
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	August 27, 2003
❖ Statistical review(s) *(indicate date for each review)*	May 15, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Sept. 3, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Aug. 28, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Chemistry Review #1 p. 21
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: June 2, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 4, 2003
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

4 Page(s) Withheld

BARR LABORATORIES, INC.

VENDOR NAME	CHECK NO.	CHECK DATE
U.S.FOOD & DRUG ADMINISTRATION		07/30/2002

DATE	INVOICE NUMBER	INVOICE AMOUNT	DISCOUNT AMOUNT	NET AMOUNT
07/30/2002	USERID4387-NDA21-544	313,320.00		313,320.00
		TOTALS		313,320.00

BARR LABORATORIES, INC.
Two Quaker Rd.
Box 2900
Pomona, NY 10970-0519
845-362-1100

MELLON GLOBAL CASH MANAGEMENT
135 SANTILLI HIGHWAY
EVERETT, MA 02149

63-282
113

CHECK NUMBER

CHECK DATE 07/30/2002

PAY THIS AMOUNT
****$313,320.00

PAY *Three hundred thirteen thousand three hundred twenty and 00/100 Dollars*

TO THE ORDER OF:
U.S.FOOD & DRUG ADMINISTRATION
PO BOX 360909
PITTSBURGH PA 15251-6909

BARR LABORATORIES, INC.

AUTHORIZED SIGNATURES

REF: NDA 21-544, USER FEE ID 4387

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

APPLICANT'S NAME AND ADDRESS

Barr Research, Inc.
One Bala Plaza, Suite 324
Bala Cynwyd, PA 19004

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
21-544

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER *(Include Area Code)*
(845) 362-1100

3. PRODUCT NAME
Seasonale®

6. USER FEE I.D. NUMBER
4387

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Christine Mundkur	Christine Mundkur Sr. Vice President, Quality and Regulatory Counsel	07/18/2002

FORM FDA 3397 (4/01)

Created by PSC Media Arts (301) 443-2454 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

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 Attached Lists	

(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
William T. McKee	Senior Vice President, CFO & Treasurer
FIRM/ORGANIZATION: Barr Laboratories, Inc.	
SIGNATURE: WTM For WTM	DATE: 7/12/02

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

Created by: PSC Media Arts (301) 443-2454 EF

SEA-301
List of Investigators

Site #	Principal Investigator	Subinvestigator (s)	Address
1	**Freedolph D. Anderson, M.D.** Ph 757-446-7102 Fax 757-446-5905 andersf@evms.edu	[redacted]	EVMS Technology Development Center 601 Colley Ave. Norfolk, VA 23507
7	**John Angelo, D.O.** Ph 504-524-2061 Fax 504-524-2120	[redacted]	New Orleans Institute of Clinical Research 2001 Canal St., Ste. 120 New Orleans, LA 70112
2	**Davis Baldwin, MD** Ph 650-324-0669 Fax 650-324-3116	[redacted]	Lifespan Research 703 Welch Road, Ste. C-3 Palo Alto, CA 94304
8	**Suzanne Barbier, MD** Ph 206-363-4555 Fax 206-522-8594 Alt Fax 206-362-2037 sbarbier@nwhsea.org	[redacted]	Women's Clinical Research Center 3216 North East 45th Place, Ste. 100 Seattle, WA 98105 1560 North 115th Street, Ste. 212 Seattle, WA 98133
22	**Saul Berg, MD** (formerly Samuel Flannagan, MD) Ph 412-363-1900 Fax 412-363-1200	[redacted]	ICSL Clinical Studies-Pittsburgh 5750 Centre Ave., Ste 230 Pittsburgh, PA 15206

Site #	Principal Investigator	Subinvestigator (s)	Address
9	**Paul Blumenthal, MD** Ph 410-550-0335 Fax 410-550-0245 pblumen@jhm.edu		4940 Eastern Ave. Dept. OB/GYN Rm. 125A1C Baltimore, MD 21224
10	**Anthony Chavez, MD** Ph 713-932-1234 Fax 713-463-8902		SMO- nTouch Ph 919-872-7223 800 Gessner Road, Suite 200 Houston, TX 77024 Ph 713-795-5975 Fax 713-795-0984
12	**Nancy Cooley, MD** Ph 952-556-2685 Fax 952-556-2688		Ridgeview Research 3000 Hundertmark Rd. Chaska, MN 55318 Western OB/GYN 550 S. Maple St. Waconia, MN 55387
13	**Jay Cooper, MD** Ph 602-249-3050 Fax 602-249-7117 whresearch@uswest.net		Women's Health Research 6036 N. 19th Ave., Ste. 400-A Phoenix, AZ 85015
14	**Vivien D'Andrea, MD** Ph 408-730-4378 Fax 408-370-3130 cmgrsrch@well.com		Camino Medical Group 301 Old San Francisco Rd. Sunnyvale, CA 94086
15	**Thomas Davies, MD** Ph 713-467-2351 Fax 713-932-7800 toptxsite1@aol.com		Med-Tech Research 8830 Long Point Road, Ste 601 Houston, TX 77055

Site #	Principal Investigator	Subinvestigator (s)	Address
17	**Edward Durbin, MD, PhD** Ph 219-288-0931 Fax 219-288-1734	[redacted]	SMO-nTouch 610 N. Michigan Street, Ste. 106 South Bend, IN 46601 Granger Family Clinic Ph 219-239-6575 52500 Fir Road Granger, IN 46530
18	**Donald Edger,MD** Ph 859-264-8999 Fax 859-264-8799	[redacted]	Central Kentucky Research Associates Inc. 2801 Palumbo Drive Suite 200 Lexington, KY 40509
19	**Robert Feldman, MD** Ph 305-665-4895 Fax 305-667-3706	[redacted]	Miami Research Associates 6280 Sunset Dr. Ste. 500 / 610 South Miami, FL 33143 100430 Overseas Hwy, Suite 300 Key Largo, FL 33037 Ph 305-451-0110
20	**Frederick D. Fingerhut, MD** Ph 623-846-7558 Fax 623-846-1674	[redacted]	Estrella Women's Health Center 4700 N. 51st Avenue, Ste 201 Phoenix, AZ 85031
21	**Frances Fisk, MI** Ph 505-243-4434 Fax 505-242-9788 obgynnet@nm.net	[redacted]	Southwest Clinical Research Medical Arts Square 801 Encino Pl, NE, Ste D-3 Albuquerque, NM 87102 NM Gynecology Consultants 801 Encino Pl, NE, Ste D-5 Albuquerque, NM 87102 Ph 505-242-5353 Fax 505-242-9788
23	**Bill Griffin,MD** Ph 361-994-5454 Fax 361-994-5455	[redacted]	5920 Saratoga Blvd., Ste 200 Spohn South Health Plaza Corpus Christi, TX 78414

Site #	Principal Investigator	Subinvestigator (s)	Address
24	**Charles Herring, MD** Ph 910-799-5500 Fax 910-799-1002 nhmra@piedmontmedical.com	[redacted]	New Hanover Medical Research 4302 Holly Tree Road Wilmington, NC 28401
25	**Andrew Kaunitz,MD** Ph 904-549-3271 Fax 904-549-3124 andrew.kaunitz@jax.ufl.edu	[redacted]	Women's Health Research 3627 University Blvd. S., Ste 355 Jacksonville, FL 32216
3	**Irwin Kerber, MD** Ph 214-341-1044 Fax 214-341-0144	N/A	Alpha Omega Clinical Research 12989 Jupiter Rd., Ste 101 Dallas, TX 75238
26	**Rebecca Knight, MD** Ph 309-672-1910 Fax 309-672-1232	[redacted]	SMO-nTouch 222 North East Monroe, Ste 904 Peoria, IL 61602
6	**Karen Kreutner, MD** Ph 843-723-4949 Fax 843-723-7108	N/A	71-A Bull St. Charleston, SC 29401
28	**James Lackey, MD** Ph 405-949-3470 Fax 405-949-3474	[redacted]	Lynn Health Science Institute 5300 N. Independence, Ste 130 Oklahoma City, OK 73112 4517 Memorial Cr. Oklahoma City, OK 73142 Lakeside Renaissance Women's Hospital 11200 N. Portland Oklahoma City, OK 73120
29	**Sooji Lee-Rugh, MD** Ph 703-930-0553 Fax 703-527-0780 harugh@erols.com	[redacted]	SMO-Millennium Research 3801 N. Fairfax Dr., Ste 11 Arlington, VA 22203 3700 Joseph Seiwick Drive, Suite 207 Fairfax, VA 22033

Site #	Principal Investigator	Subinvestigator (s)	Address
30	**Thomas Littlejohn, MD** Ph 336-768-8062 Fax 336-760-2957	[redacted]	Piedmont Medical Research Associates 1901 South Hawthorne Road, Ste 306 Winston-Salem, NC 27103 755 Highland Oaks Drive, Suite 201 Winston Salem, NC 27103
31	**James Maly, MD** Ph 402-434-3370 Fax 402-489-0249 wcolcr@aol.com	[redacted]	Women's Clinic of Lincoln, PC 220 Lyncrest Drive Lincoln, NE 68510
32	**Phyllis Marx, MD** Ph 312-494-2227 Fax 312-494-2237 csynecki@protocare com	[redacted]	SMO-Protocare 515 North State St., Ste 2700 Chicago, IL 60610
33	**Marjorie Merod, MD** Ph 919-781-2514 Fax 919-420-6067	[redacted]	Wake Research Associates 3100 Blue Ridge Road, Ste 200 Raleigh, NC 27612 Obstetrics, Gynecology, & Fertility 2801 Blue Ridge Road, Suite G-50 Raleigh, NC 27607 Capital Area Obstetrics & Gynecology, PA Rex Family Center 4420 Lake Boone Trail Raleigh, NC 27607
39	**Paul Miller, MD** Ph 864-455-8488 Fax 864-455-3095 tprice@ghs.org	[redacted]	Center for Women's Medicine Research 890 W. Faris Rd., Ste 470 Greenville, SC 29605
4	**Alfred Moffett, MD** Ph 352-787-1535 Fax 352-315-0606 heinold@aol.com	N/A	Medical Plaza 401 601 East Dixie Avenue Leesburg, FL 34748
34	**David Morin, MD** Ph 423-989-3105 Fax 423-989-3693 www.piedmontmedic al.com	[redacted]	TriCities Medical Research Associates 321 Midway Medical Park, Ste 3 Bristol, TN 37620

#	Investigator		
36	**Anjuli Nayak, MD** Ph 309-671-8378 Fax 309-693-7152 Asthma2@aol.com	[redacted]	Falcon Center for Women 9000 N. Lindbergh Dr. Suite B Peoria, IL 61615 5401 Knoxville Ave, Suite 134 Peoria, IL 61614
37	**Robert Nett, MD** Ph 210-614-7483 Fax 210-614-4524 rnett@protocare.com	[redacted]	SMO-Protocare San Antonio Center for Clinical Research 8122 Datapoint, Ste 1010 San Antonio, TX 78229
48	**Arthur Pitterman, MD** Ph 702-254-3131 Fax 702-254-3244	[redacted]	400 Shadow Lane, Suite 110 Las Vegas, NV 89106 Caring for Women 3201 Maryland Parkway, Ste. 300 Las Vegas, NV 89109 Ph 702-254-3131 Fax 702-254-3244
38	**David Portman, MD** Ph 614-861-6707 Fax 614-861-6335 ccwhr@earthlink.net	[redacted]	The Columbus Center for Women's Research 5965 E. Broad St., Ste 110 Columbus, OH 43213
50	**Robert E. Prout, MD** Ph 508-398-4500 Fax 508-398-4504	[redacted]	ICSL Clinical Studies 23H White's Path South Yarmouth, MA 02664
40	**George Raad, MD** Ph 704-527-6672 Fax 704-527-4622	[redacted]	Metrolina Medical Research Associates 1700 Abbey Place, Suite 209 Charlotte, NC 28209 Park Road Medical Clinic 4444 Park Rd. Charlotte, NC 28209
35	**David Rayl , MD** Ph 757-594-4729 Fax 757-594-3835	[redacted]	Riverside OB-GYN 316 Main Street, 2nd Floor Newport News, VA 23601
41	**Sidney Rosenblatt, MD** Ph 949-753-1663 Fax 949-753-4761 srosenblatt@protocare.com	[redacted]	SMO-Protocare Irvine Center for Clinical Research 16259 Laguna Canyon Rd. Irvine, CA 92618

Site #	Principal Investigator	Subinvestigator (s)	Address
42	**Mark Shepard, MD** Ph 202-345-6439 Fax 202-429-4341	[redacted]	SMO-Millennium Research 2021 K Street NW #310 Washington, DC 20006
5	**James A. Simon, MD** Ph 301-953-9677 Fax 410-792-7468 jasimon@erols.com	[redacted]	Women's Health Research Center 14201 Laurel Park Drive, Ste 104 Laurel, MD 20707
43	**John Stoukides,MD** Ph 401-435-8950 Fax 401-435-8956	[redacted]	ICSL-Clinical Studies 40 Hemingway Drive East Providence, RI 02915
44	**Michael Swor, MD** Ph 941-342-8288 Fax 941-378-8320	[redacted]	ICSL Clinical Studies-Sarasota 5969 Cattleridge Blvd., Ste 100 Sarasota, FL 34232 1617 South Tuttle Ave., 1A Sarasota, FL 34239 Ph 941-330-8885 Fax 941-906-8774
45	**Timothy Truitt, MD** Ph 321-984-9176 Fax 321-984-9146 nashr@healthadvance.com	[redacted]	SMO-nTouch 2202 South Babcock St., Ste 101 Melbourne, FL 32901 5305 Babcock St., NE Ph 321-676-9009 Palm Bay, FL 32905 OMNI Healthcare Ph 321-768-6363 1344 Apollo Blvd Melbourne, FL 32901

Site #	Principal Investigator	Subinvestigator (s)	Address
46	**Wulf Utian, MD** Ph 440-460-2400 Fax 440-460-2278 Utian@rapidmedical research.com	[redacted]	Rapid Medical Research, Inc. 29001 Cedar Rd., Ste 202 Cleveland, Oh 44124
47	**Cheryl Walker, M Lynn Westphal, MD** Ph 650-725-9977 Fax 650-498-4320	[redacted]	Stanford University School of Medicine Dept. of Gynecology and Obstetrics 300 Pasteur Dr. Boswell Building HH333 Stanford, CA 94305-5317
49	**John Willems, MD** Ph 858-554-8690 Fax 858-554-8727	[redacted]	Scripps Clinic 10666 North Torrey Pines Rd. MD MS314 La Jolla, CA 92037

Bioavailability/Bioequivalence Studies
List of Investigators

Site	Principal Investigator (s)	Sub-investigator (s)	Address
Novum	So Ran Hong, M.D.*	[redacted]	Novum Pharmaceutical Research Services 11248 Wilcrest Green Houston, TX 77042
Anapharm	Eric Masson, Pharm.D.**	[redacted]	Anapharm Inc. 2050, boul. Rene-Levesque Quest Sainte-Foy (Quebec) G1V 2K8 Canada Anapharm Inc. 5467 bout. Des Forges Trois-Rivieres (Quebec) G8Y 5L5 Canada

* The same Principal Investigator and site were used for study #'s 10116208, 10216205, & 10216206.
** The same Principal Investigator and site were used for study #'s 99027 & 99028.

Attachment to Form 3454

[redacted]

The financial certification documentation from sub-investigator [redacted] of site 48 was obtained at the time of her initiation in the study and was filed at the site. However, due to Dr. Pitterman's departure from ICSL, some personnel were laid off and files have been archived at off-site storage facility. During this transition, this documentation has been misplaced. The CRO, [redacted] has taken initiative to search the archives to locate the information and to contact the investigator. Therefore, Barr has acted due diligently to obtain the information required under 21 CFR 54.4 from the investigator. A separate financial certification (Form 3454) for Ms. [redacted] is provided.

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

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

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study SEA-301, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of clinical study

Please mark the applicable checkboxes.

- ☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- ☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- ☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;
- ☐ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
William T. McKee	Senior Vice President, CFO & Treasurer
FIRM/ORGANIZATION	
Barr Laboratories, Inc.	
SIGNATURE	DATE
FOR WTM	7/12/02

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 4 hours 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:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

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

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

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study SEA-301, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

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Please mark the applicable checkboxes.

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— any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

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NAME	TITLE
William T. McKee	Senior Vice President, CFO & Treasurer
FIRM/ORGANIZATION	
Barr Laboratories, Inc.	
SIGNATURE	**DATE**
FOR WTM	7/12/02

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Name of clinical study

Please mark the applicable checkboxes.

— any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

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— any proprietary interest in the product tested in the covered study held by the clinical investigator;

— any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
William T. McKee	Senior Vice President, CFO & Treasurer
FIRM/ORGANIZATION	
Barr Laboratories, Inc.	
SIGNATURE	DATE
For WTM	7/12/02

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Department of Health and Human Services
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Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Form Approved: OMB No. 0910-0396
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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		

☐ (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
William T. McKee	Senior Vice President, CFO & Treasurer
FIRM/ORGANIZATION: Barr Laboratories, Inc.	
SIGNATURE: FOR WTM	DATE: 7/12/02

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

FORM FDA 3454 (3/99)

18 Page(s) Withheld

1 NDA 7/12/02

NDA: 21-544 Seasonale® by Barr Research

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	One		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		No bookmarks were provided for each category of electronic Individual Patient Data Listings
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?			N/A
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		Case report forms were submitted electronically. It was not verified if each required case report forms was submitted.
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?			N/A
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		

ITEM	YES	NO	COMMENT
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

Brenda S. Gierhart, MD/ September 6, 2002
Reviewing Medical Officer / Date

Scott Monroe/
Supervisory Medical Officer/Date

NDA 21-544: Filing Meeting Clinical Comments
September 9, 2002

Drug: Seasonale® Tablets (91-day extended oral contraceptive regimen);

Sponsor: Barr Research
Dose: 84 pink active levonorgestrel and ethinyl estradiol tablets 0.15 mg/0.03 mg followed by 7 white placebo tablets)
Indication: Prevention of pregnancy

Background: Seasonale is a novel 91-day oral contraceptive regimen utilizing the same combination levonorgestrel and ethinyl estradiol active tablets as in Nordette® Tablets 21 days and 28 days (Wyeth-Ayerst's NDA 18-668 and NDA 18-782) and as in Portia, the generic equivalent of Nordette (Barr's ANDA 78-866 approved on May 23, 2002). According to the sponsor, there are no product approvals worldwide for an oral contraceptive regimen beyond 28 days using levonorgestrel and ethinyl estradiol tablets (Volume 2 Section 3.3: Foreign Marketing History on pg. 03-000050).

Pediatric: Barr has requested a full waiver of all pediatric studies since according to class labeling, the safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age and are expected to be the same for postpubertal adolescents under the age of 16 and for 16 years and older. Barr intends to label the product: Use of this product before menarche is not indicated.

Trade name: A tradename review for Seasonale (levonorgestrel/ethinyl estradiol) was consulted to Ms. Sammy Beam, Associate Director, Medication Error Prevention, OPDRA by DRUDP on June 25, 2001.

Exclusivity: Barr is claiming a period of 3 years of marketing exclusivity for Seasonale.

Efficacy and Safety studies: Barr submitted the results of three trials: Study SEA-301, Study 99028, and Study 10216206.

- Study **SEA-301** is stated by the sponsor to be an adequate and well-controlled trial that provides substantial evidence of effectiveness of Seasonale to prevent pregnancy.
- Study **99028** is the bioavailability/bioequivalence (BA/BE) trial previously submitted to support approval of Portia (ANDA 75-866); it is a randomized, single-dose, 3-way crossover, fasting BE study comparing pink Portia tablets to Nordette (USA) and Min-Ovral (Canada) in 30 healthy female subjects (29 completers)
- Study **10216206** is the bridging bioequivalence study comparing the proposed commercial generic Nordette formulation (pink active tablets) and the Seasonale formulation : active tablets) dosed in SEA-301; it is a randomized, single-dose, fasting, 2-way crossover BE study in 30 healthy female subjects (30 completers).

The sponsor listed ten supportive clinical studies: the Nordette clinical study described in the Medical Officer Review of NDA 18-668 dated 5/10/82 and nine published articles on extended oral contraceptive dosing regimens (i.e. longer than 28 days).

The sponsor listed three supportive BA/BE studies: Study 99027 (a randomized, fasting, 2-way crossover study in 35 women with 30 completers comparing Seasonale Ultra-LO and Levlite tablets), Study 10216205 [a randomized, single-dose, fasting 2-way crossover BE study comparing white tablets with revised [redacted] formula [redacted] and the Seasonale [redacted] active tablets dosed in SEA-301 in 30 healthy female subjects with 30 completers], and Study 10116208 (a fasting 2-way BE study comparing [redacted] tablets with revised [redacted] formula and [redacted] active tablets dosed in SEA-301 in 30 healthy female subjects with 29 completers).

SEA-301 was a multicenter (47 sites) four-arm, parallel group, 2:2:1:1 randomized, open-label, one-year treatment duration clinical trial comparing the efficacy and safety of Seasonale LO (464 women), Seasonale Ultra-LO (467 women), Nordette (230 women) and Levlite (233 women). Approval of Seasonale Ultra-LO (84 active levonorgestrel and ethinyl estradiol tablets 0.1 mg/0.02 g followed by 7 placebo tablets) has not been requested. The subjects in SEA-301 were generally healthy women aged 18-40 who desired pregnancy prevention. All patients completed electronic diaries daily to assess compliance, bleeding or spotting, and menstrual-related symptoms. A total of 148 women were enrolled in an endometrial biopsy cohort. The primary comparison will be made on the 694 women randomized to Seasonale or Nordette. A two-year extension to gather further safety data (SEA-301A) was begun in September 1, 2001.

SEA-310 Efficacy Issues:

- Limited exposure to Seasonale LO
  - 464 subjects were randomized to Seasonale LO.
  - 456 were treated with Seasonale LO for a total of 4143.75 patient months (each patient month was 28 days)
  - 268 patients on Seasonale LO completed the 12-month study.
- Barr originally and erroneously defined pregnancy as a positive pregnancy test with confirmation by ultrasound; pregnancies are to be defined as a positive pregnancy test regardless of ultrasound findings. It is unclear if Barr corrected their error after this was pointed out to them during the April 23, 2002 teleconference.
- 169 women in SEA-301 (59 on Seasonale LO and 30 on Nordette) will be excluded from the primary efficacy analysis due to being aged 36-40 years. Additional cycles of exposure were eliminated from the efficacy analysis due to concurrent use of a second form of contraceptive. With so many patients and cycles of exposure excluded from the primary efficacy analysis, is there enough efficacy data remaining to support approval?
- Pearl Rates were significantly higher than in previous studies for Nordette and Levlite. The daily reminders to record in the electronic diaries should have improved the compliance when compared to previous Nordette and Levlite studies.
- Only 106 of the 1394 randomized subjects in SEA-301 were "fresh starts"; 35 of the 106 "fresh starts" were exposed to Seasonale LO. About 61 % of all study participants were continuous OC users and about 30% were prior OC users. Can product be adequately labeled as appropriate for "fresh starts"?

Table 1: Pregnancies reported while on active treatment among participants who received at least one dose of treatment (ITT)

	Seasonale Lo	Nordette	Seasonale Ultra-Lo	Levlite
# Subjects Treated (ITT)	456	226	463	231
/# 28-day patient months*	4143.75	2376.00	4091.75	2358.00
/Pearl Index	1.25	1.64	2.22	3.31
# Subjects Treated (ITT) aged 18-35	395	193	410	209
/# 28-day patient months*	3090.75	1752.00	2934.75	1767.00
/# cycles**	951	1752	903	1767
/Pearl Index	1.68	2.23	3.10	3.68
# on-treatment pregnancies among ITT Subjects	5	3	9	6
# on-treatment pregnancies among ITT subjects aged 18-35 years	4	3	7	5

Note: it is unclear if these are pregnancies as defined by Barr as positive pregnancy tests confirmed by sonogram OR pregnancies as defined by HFD-580 as positive pregnancy tests

*Number of completed 28-day patient months--after excluding months when another BCM was used

**Number of completed cycles only--after excluding cycles when another BCM was used

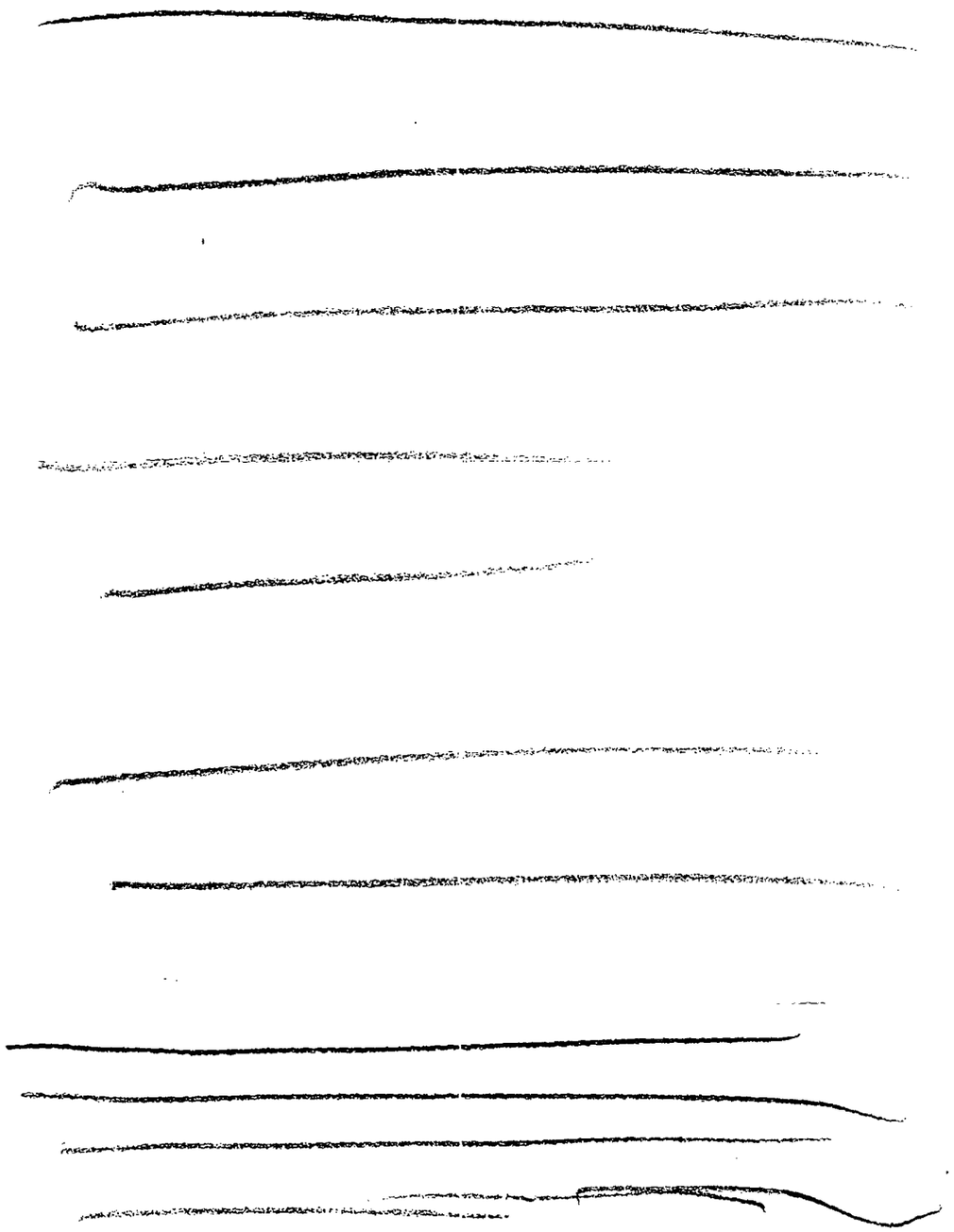
SEA-310 Safety Issues:

- Menorrhagia occurred more frequently in the Seasonale LO (11.62%) and the Seasonale Ultra LO (14.90%) arms than in the Nordette (2.65%) and the Levlite (2.60%) arms. Increased risk of irregular bleeding and increased risk of pregnancy without much benefit may prevent approval.
- 89 sets of baseline and 12 months endometrial biopsies were obtained: only 38 sets were from the Seasonale LO arm. Coordination of the evaluation of biopsy findings was done at the Eastern Virginia Medical School under Freedolph Anderson, MD. The endometrial biopsy reports issued by each of the three pathology reviewers could not be located in the NDA. On September 6, 2002 the sponsor was asked to provide the location of these reports in the NDA.
- Overall, 40.6 % of the ITT patients on Seasonale LO discontinued versus only 28.8% of the ITT patients on Nordette. Significantly more women discontinued use of Seasonale LO (14%) or Seasonale Ultra-LO (19%) due to an adverse event than did subjects on Nordette (9%) or Levlite (8%). Specifically, significantly more women discontinued due to menorrhagia in the Seasonale LO (n=26; 5.7%) and Seasonale Ultra LO (n=42; 9.1%) groups than in the Nordette (n=4; 1.8%) and Levlite (n=1; 0.4%) groups. In addition, a larger proportion of patients discontinued from the study due to "unacceptable bleeding" in the Seasonale LO (n=35; 7.7%) and Seasonale

Ultra LO (n=64; 13.8%) groups than in the Nordette (n=4; 1.8%) and Levlite (n=2; 0.9%) groups.

- Submission Serial No. 026 dated 6/8/01 reported on a 39 year old hospitalized for a pulmonary emboli (Mfr. report 01-107-SEAS-13) while on Seasonale Lo; "likely" relationship to drug; additional information submitted on 6/28/01 and in Serial No. 033 on 7/19/01.

DSI:



Additional Issues:

1) It should be noted that the sponsor failed to sequentially number each page in Volume 1. The sequential page numbering in Vol. 1 stops in the middle of Item 12 after page 02-0000193 and no page numbering is provided for the Item 12 package labeling. Items 13-20 in Volume 1 either have no page numbering or numbering beginning with "page 1" at the beginning of the Item. On September 6, 2002 the sponsor was asked to provide sequential page numbering for Volume 1.
2) The Financial Disclosure section (Vol. 1 Item 19) is confusing since there are no page numbers and the supporting information does not immediately follow the pertinent Form FDA 3454. On September 6, 2002, the sponsor was asked to clarify which pages of supporting information are related to each FDA 3454 form.

Recommendation regarding filing:

1) Although the reviewer has identified multiple efficacy and safety issues with NDA 21-544, they are all considered review issues. In particular regarding the number of subjects exposed to Seasonale LO, the Division generally requests for a new hormonal contraceptive product that a sponsor submit clinical data from 200 women treated for at least one year as well as clinical data from women treated for at least 10,000 treatment months. In NDA 21-544 for Seasonale LO, the sponsor provided data for at least 200 women treated for at least one year and for approximately 4000 treatment months. Since Seasonale LO is a new regime for an approved oral contraceptive tablet and not a new molecular entity, the reviewer recommends filing the NDA and assessing the adequacy of the data during the review cycle.
2) From a clinical perspective, NDA 21-544 is fileable.

Brenda S. Gierhart, MD
Medical Officer
Division of Reproductive and Urologic Drug Products

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY NDA FILEABILITY CHECKLIST

NDA: 21-544 **Applicant:** Barr Research, Inc. **Stamp Date:** 5-AUG-2002

Drug Name: Seasonale (levonorgestrel and ethinyl estradiol tablets, USP) 0.15 mg/0.03 mg

IS THE CMC SECTION OF APPLICATION FILEABLE? YES

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Reference is made to ANDA 75-866.
8	Does the section contain controls for the drug product?	X		Reference is made to ANDA 75-866.
9	Has stability data and analysis been provided to support the requested expiration date?	X		Per FDA's agreement on 23-APR-2002, stability data are provided for three batches of the OGD-approved Portia.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		Reference is made to ANDA 75-866.
14	Is there a Methods Validation package?	X		Reference is made to ANDA 75-866.
15	Is a separate microbiological section included?			Not applicable. This is a tablet dosage form.

Comments:

- The drug product subject of this NDA 21-544 is the same as the marketed Portia, which was approved by the Office of Generic Drug on 23-MAY-2002 under ANDA 75-866.
- The approved ANDA product is packaged for a 28-day regimen, while the NDA product is packaged for a 91-day regimen. The primary packaging is the same for both products.
- The applicant is the same for both products.
- The ANDA is cross-referenced for all CMC information. Per FDA's agreement on 23-APR-2002, stability data are provided for three batches of the ANDA product to support the expiry of the NDA product.

- The only difference between the NDA product and the approved ANDA product is the code debossed on the tablet. For the NDA, the active tablet is debossed with "S" on the top and "62 [redacted]" on the bottom, and the placebo is debossed with "S" on the top and [redacted]197" on the bottom. For the approved ANDA, the active tablet is debossed with "B" on the top and "992" on the bottom, and the placebo is debossed with "B" on the top and "208" on the bottom.

Review Chemist: /S/ Date:

Team Leader: Date:
cc: Original NDA 21-544
HFD-580/Division File
HFD-580/JMercier/STran/MRhee

Have all DMF References been identified? YES

DMF #	TYPE	HOLDER	ITEM REFERENCED
[redacted]	II	[redacted]	[redacted]
[redacted]	II	[redacted]	[redacted]
[redacted]	III	[redacted]	[redacted]
[redacted]	III	[redacted]	[redacted]

DRUG PRODUCT NAME
Proprietary: Seasonale
Nonproprietary/USAN: levonorgestrel and ethinyl estradiol tablets, USP

APPLICANT:
Barr Research, Inc.

PHARMACOL. CATEGORY/INDICATION oral contraceptive

DOSAGE FORM: immediate-release tablets

STRENGTHS: 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol

ROUTE OF ADMINISTRATION oral administration

DISPENSED: X Rx _____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

3 Page(s) Withheld

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

/s/

Suong Tran
9/9/02 02:13:33 PM
CHEMIST

paper signed 8/26/02

Moo-Jhong Rhee
9/9/02 03:45:30 PM
CHEMIST
I concur

16 Page(s) Withheld