DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
The R.W. Johnson Pharmaceutical Research Institute	16 NOV 2001
TELEPHONE NO. (*Include Area Code*)	**FACSIMILE (FAX) Number (*Include Area Code*)**
(908) 704-4812	(908) 203-1499

APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):

920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-180

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
norelgestromin and ethinyl estradiol	ORTHO EVRA™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
transdermal patch	150 mcg norelgestromin 20 mcg ethinyl estradiol	Transdermal

(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

APPLICATION INFORMATION

APPLICATION TYPE (*check one*) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (*check one*) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION RESPONSE TO FDA REQUEST TO PROVIDE ADDITIONAL FINANCIAL DISCLOSURE INFORMATION

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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This application contains the following items: (*Check all that apply*)		
☐	1. Index	
☒	2. Labeling (check one)	☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
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☐	18. User Fee Cover Sheet (Form FDA 3397)	
	19. Financial information (21 CFR Part 54)	
	20. OTHER (Specify)	

CERTIFICATION

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3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Valerie A Pompa for	Ramon Polo, PhD Director, Regulatory Affairs	16 NOV 2001

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602	(908) 704-4812

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artment of Health and Human Services
..od and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 U.S. Route # 202, P.O. Box 300
Raritan, New Jersey 08869-602

TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499

DATE: *16 November 2001*

TO: *JENNIFER MERCIER*
Project Manager, FDA
Div. Reprod. & Urol. Drug Products

TELEFAX #: *(301) 827-4267*

FROM: Valerie Donnelly
Regulatory Affairs
Phone: (908) 704-5891
Fax: (908) 203-1499

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 5
NOTE: If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

MESSAGE (If any):

JENNIFER,
RE: NDA 21-180 ORTHO EVRA™ dissolution specifications
ATTACHED IS A FAXED VERSION OF OUR RESPONSE TO FDA'S REQUEST THAT WE REVISE THE DISSOLUTION SPECS. A hard copy submission will follow tomorrow morning. f you have additional questions or comments on this submission, please call me at (908) 704-5891. THANKYOU

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

faxed NOV 16, 01

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Response to FDA Request For CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the 15 November 2001 teleconference with the Division to discuss the dissolution specifications for the drug product. FDA's requested RWJPRI to revise the specifications submitted in the NDA to the new specifications calculated by FDA.

Test Attribute	Old NDA Specification	New Interim FDA calculated Specification
Drug Release		
a) Norelgestromin (NGMN)		
b) Ethinyl estradiol (EE)		

RWJPRI agrees to accept the interim specifications above, as calculated by FDA. We will re-test the lots in stock according to the new specifications calculated by FDA. We also agree with the proposal to come back to the Agency as soon as we have additional data on production batches and a justification for setting new specifications.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send desk copies to:
Dr. Mhoojong Rhee - FDA/DRUDP/HFD-580, Chem-pharm Team Leader
Dr. Amit Mitra - FDA/DRUDP/HFD-580, Chemistry Reviewer
Dr. Dhruba Chatterjee - FDA/DRUDP/HFD-580, Biopharm Reviewer

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602	

PRODUCT DESCRIPTION

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ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
norelgestromin and ethinyl estradiol	ORTHO EVRA™
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	**CODE NAME (*If any*)**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
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(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

APPLICATION INFORMATION

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CERTIFICATION

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Faxed Nov 16 01

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Ramon Polo, PhD **Director, Regulatory Affairs**	

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 **Raritan, New Jersey 08869-0602**	**(908) 704-4812**

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1401 Rockville Pike
Rockville, MD 20852-1448

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FORM FDA 356h (4/00)

1

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 Route 202, P.O. Box 300 Raritan, NJ 08869-0602

Fax Cover Sheet

Date:	November 16, 2001	**Pages:**	
To:	Jennifer Mercier	**From:**	Karen Futterknecht K-F.
Dept.:	FDA	**Dept.:**	Regulatory Affairs
Fax #:	301-827-4267	**Fax #:**	908-722-5113
Telephone #:	301-827-4249	**Telephone #:**	908-704-4912

Comments:

APPEARS THIS WAY
ON ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

16 NOV 2001

Susan Allen, MD, Director
Division of Reproductive and Urologic
Drug Products HFD-580

Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-04

5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

AMENDMENT TO A PENDING APPLICATION:
Labels/Labeling Information and

Dear Dr. Allen:

Reference is made to our pending NDA 21-180 for ORTHO EVRA™ and to the draft package components submitted with the original application on 20 December 2000 NDA (Item 2, Item Volume 1, Pages 52-59). Reference is also made to the draft packaging components that were amended to the pending application on 05 October 2001. At this time we would like to amend the NDA to withdraw the ——— component. Attached is a black and white copy of the component.

If you have questions regarding this information please contact me at (908)-704-4812 or Valerie Donnelly at (908)-704-5891 or our dedicated number for FDA use (908)-704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Valerie L Donnelly for /

Ramon Polo Ph.D.
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist
Fax Copy to Jennifer Mercier

N:cygnus\ltr\10050\package comp amend for packer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*)

DOSAGE FORM:
transdermal patch

STRENGTHS:
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20 mcg ethinyl estradiol

ROUTE OF ADMINISTRATION:
Transdermal

(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

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☐	19. Financial Information (21 CFR Part 54)	
	20. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Valerie A Donnelly for	Ramon Polo, PhD Director, Regulatory Affairs	16 NOV 2001

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602	(908) 704-4812

Public reporting burden for this collection of information is estimated to average 40 hours 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:

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

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.

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

faxed to FDA 13 Nov 2001 (VM)

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Response to FDA Request for Chemistry, Manufacturing and Controls (CM&C) Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to our teleconference with the Division on 09 November 2001. During this teleconference, FDA requested the following:

- **The proposed 8-hour dissolution specifications are too wide. An Excel spreadsheet containing the data from clinical batches 01107, 01517 and 01607 is requested.**
- **The development history for the dissolution method is requested. Specifically, we are interested in your rationale for the choice of medium and pH utilized in the specification.**

Our responses and supporting data are provided behind the tabs entitled "Responses", "Appendix 1" and "Appendix 2". We have provided the best quality copies available. In addition, we have enclosed the Excel spreadsheet data on a diskette and forwarded an electronic copy via email to Jennifer Mercier, Project Manager, DRUDP. The diskettes were scanned using McAfee virus shield version V.4.5.0.534, virus definition 4.0.4169, scan engine 4.1.40 and deemed to be virus-free.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send desk copies to:
1. Dr. Amit Mitra, Chemistry Reviewer
2. Dr. Dhruba J. Chatterjee, Biopharm. Reviewer
FDA/DRUDP
HFD-580
Rockville, MD 20857
Phone No. (301) 827-4260

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
The R.W. Johnson Pharmaceutical Research Institute	
TELEPHONE NO. (*Include Area Code*)	**FACSIMILE (FAX) Number (*Include Area Code*)**
(908) 704-4812	(908) 203-1499
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE**
920 Route 202 South P.O. Box 300 Raritan, New Jersey 08869-0602	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-180

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
norelgestromin and ethinyl estradiol	ORTHO EVRA™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) — CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
transdermal patch	6 mg norelgestromin 0.75 mg ethinyl estradiol	Transdermal

(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

APPLICATION INFORMATION

APPLICATION TYPE (*check one*): ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*) ☐ ORIGINAL APPLICATION ■ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☒ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION RESPONSE TO FDA REQUEST FOR CMC INFORMATION

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, EMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
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☐	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
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☐	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (k) (3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Ramon Polo for	Ramon Polo, PhD Director, Regulatory Affairs	faxed 13 NOV 2001

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 Raritan, New Jersey 08869-0602	(908) 704-4812

FAXED in 2 PARTS ① PAges 1 (letter) – 22 + cover sheet ② 23 – 44 + cover sheet.

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 U.S. Route # 202, P.O. Box 300
Raritan, New Jersey 08869-602

TELEFACSIMILE TRANSMITTAL FORM

FAX NUMBER: (908) 203-1499

VAD

DATE: *13 November 2001*

TO: *JENNIFER MERCIER*
Project Manager, FDA
Div. Reprod. & Urol. Drug Products

FROM: Valerie Donnelly
Regulatory Affairs
Phone: (908) 704-5891
Fax: (908) 203-1499

TELEFAX #: *(301) 827-4267*

NUMBER OF PAGES (INCLUDING TRANSMITTAL FORM): 44 TOTAL
plus 2 cover sheets

NOTE: If you do not receive the correct number of pages or if the transmission is unclear, please call me at (908) 704-5891.

MESSAGE (if any):

JENNIFER,
RE: NDA 21-180 ORTHO EVRA™ dissolution date
ATTACHED IS A FAXED VERSION OF OUR RESPONSE TO THE AGENCY'S 09 NOVEMBER 2001 REQUEST TO PROVIDE ADDITIONAL CM&C INFORMATION. A hard copy submission will follow tomorrow morning. If you have additional questions or comments on this submission, please call me at (908) 704-5891. THANKYOU

Mailed

FAXED 11/2/01 and 11/5/01 (VAD)

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

DESK COPY

02 NOV 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 18 October 2001 email request. The FDA question appears below in bold face type and the RWJPRI response appears below it.

Question: Does the sponsor have any data information regarding the residual amount of drug content in the patches after use (7 days), or any data that indicates what % of the loaded drug is released from the patch on to the skin in 7 days (not just what is bioavailable)?

Response:

Tables 1-3 show the data requested by the reviewer. The data were generated by analyzing patches from human subjects for norelgestromin (NGMN) and ethinyl estradiol (EE), after the patches had been worn for 7 days. The apparent quantity of drug delivered (in % Formula Strength) was calculated by subtracting the quantity of drug remaining in the patch from the quantity in the control (unused patches). For study NRGEEP-PHI-003, the quantity of drug in the control patches was determined in a separate assay while for studies NRGEEP-PHI-004 and NRGEEP-PHI-005, the batch release assay values were used as the "control."

Tables 1-3 show the data available from the three studies cited above after 7 days of treatment. For studies NRGEEP-PHI-003 and -005, the patch was worn on the abdomen while for study NRGEEP-PHI-004, the patch was worn on different areas of the body (upper outer arm, abdomen, upper torso or buttock) as indicated in Table 2.

On examination of the data, it is clear that there is considerable variability in the data for apparent amounts of each drug delivered. For example, considering only the abdomen as the application site, the average apparent amounts of drug delivered (in the three studies) range from 164.6 to 276.9 μg/day for NGMN and from 29.9 to 42.9 μg/day for EE. When one includes the standard deviations, the range is 119.2 to 387.5 μg/day for NGMN and 19.1 to 60.9 μg/day for EE. Therefore, it is difficult to draw any firm conclusions on the true amount of drug delivered to the systemic circulation from these data. Our opinion is that the calculated apparent amount of drug delivered is, at best, a crude method of determining how much drug is actually delivered from the patch to the surface of the skin and does not reflect either the absolute dose delivered to the systemic circulation or the relative dose comparable to an oral contraceptive tablet.

At the time these determinations were done, they were being used as a development tool to help assess our progress in achieving the target quantities of actives in the patch and in the systemic circulation. They were not done in an attempt to achieve mass balance, which is a much more demanding and difficult exercise. For example, the skin was not swabbed and any residual adhesive collected to account for drug on the skin at the time the patch was removed. For these reasons, we are of the opinion that the data provided here represent estimates of the apparent amounts of delivered drug to the surface of the skin. and do not accurately reflect the quantity of each drug delivered into the circulation.

In the past, "difference" methods, which indirectly estimated the daily dose have been used. Doses were estimated, by difference, via subtraction of the residual amounts in the patch following removal after wear, from the amount of drug(s) present from unused patches, added to that extracted from the skin. Even with such precautions, such methods tend to be highly variable, and could lead to inaccurate estimations of the amount of drug delivered systemically. Such variability stems from the variability in patch extraction, skin extraction, and the large difference between what is actually in the patch and the small amount delivered per day.

The shortcomings of this approach were discussed with the agency on August 31, 1998 and, at the time, the more direct approach of determining the dose delivered to the systemic circulation (described in draft protocol of NRGEEP-PHI-014 submitted to the agency) was deemed acceptable. It was subsequently performed as study NRGEEP-PHI-014, a report of which was submitted in the NDA (Item 6/Item Volumes 2-3/Page1).

Table 1: Residual Drug Content Data From Study No. NRGEEP-PHI-003 (Lot 00096) Following One Week of Wear on the Abdomen

Subject[a]	% Remaining (% FS)	
	Norelgestromin	Ethinyl estradiol
Mean (sd)	79.4 (±5.3)	70.3 (±10.1)
Control (6 unused samples)	NGMN (% FS)	EE (% FS)
Mean	98.6	98.2
	NGMN (% FS)	EE (% FS)
% "delivered" in 7 days	19.2 (±5.3)	27.9 (±10.1)
	NGMN (µg)	EE (µg)
Amount "delivered" per day	164.6* (±45.4)	29.9** (±10.8)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

* Sample calculation: 19.2 x 6000 µg/(100 x 7 days) = 164.6 µg/day

** Sample calculation: 27.9 x 750 µg/(100 x 7 days) = 29.9 µg/day

Table 2: Residual Drug Content Data From Study No. NRGEEP-PHI-004 (, Following One Week of Wear

Subject[a]	% Remaining (% FS)							
	Norelgestromin				Ethinyl estradiol			
	Outer Arm	Abdomen	Torso	Buttock	Outer Arm	Abdomen	Torso	Buttock
Mean (sd)	67.1 (±7.9)	65.6 (±12.9)	62.8 (±11.8)	65.2 (±8.4)	56.0 (±10.4)	55.4 (±16.8)	50.4 (±14.4)	52.9 (±13.5)
Control (Batch Release)	NGMN (% FS)				EE (% FS)			
Assay Result	97.9%				95.4%			
	NGMN (% FS)				EE (% FS)			
% "delivered" in 7 days	30.8 (±7.9)	32.3 (±12.9)	35.1 (±11.8)	32.7 (±8.4)	39.4 (±10.4)	40.0 (±16.8)	45.0 (±14.4)	42.5 (±13.5)
	NGMN (µg)				EE (µg)			
Amount "delivered" per day	264.0 (±67.7)	276.9 (±110.6)	300.9 (±101.2)	280.3 (±72.0)	42.2 (±11.2)	42.9 (±18.0)	48.2 (±15.4)	45.5 (±14.5)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.
[b] Patient 37 replaced Patient 21, who withdrew from the study.
ND = Not Determined

Table 3: Residual Drug Content Data From Study No. NRGEEP-PHI-005 Lot 00636) Following One Week of Wear on the Abdomen

Subject[a]	% Remaining (% FS)	
	Norelgestromin	Ethinyl estradiol
Control (Batch Release)	NGMN (% FS)	EE (% FS)
Assay Result	97.9	95.4
	NGMN (% FS)	EE (% FS)
% "delivered" in 7 days	29.7 (±5.8)	35.8 (±7.7)
	NGMN (µg)	EE (µg)
Amount "delivered" per day	254.6 (±49.7)	38.4 (±8.2)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

APPEARS THIS WAY
ON ORIGINAL

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to Dr. Dhruba J Chatterjee, FDA/DRUDP/HFD-580

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
The R.W. Johnson Pharmaceutical Research Institute	**02 NOV 2001**
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(908) 704-4812	**(908) 203-1499**
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
920 Route 202 South **P.O. Box 300** **Raritan, New Jersey 08869-0602**	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 21-180**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
norelgestromin and ethinyl estradiol	**ORTHO EVRA™**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*) | CODE NAME (*If any*)

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
transdermal patch	**6 mg norelgestromin** **0.75 mg ethinyl estradiol**	**Transdermal**

(PROPOSED) INDICATION(S) FOR USE:
Prevention of Pregnancy

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (*check one*) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION **RESPONSE TO FDA REQUEST FOR INFORMATION**

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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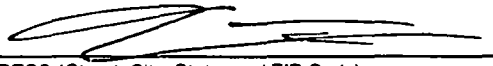
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	**Ramon Polo, PhD** **Director, Regulatory Affairs**	0 2 NOV 2001

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
920 Route 202 South, P.O. Box 300 **Raritan, New Jersey 08869-0602**	**(908) 704-4812**

Public reporting burden for this collection of information is estimated to average 40 hours 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

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.

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

Amendment to a Pending Application:
Request for Marketing Exclusivity

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin and ethinyl estradiol transdermal system. Reference is also made to 21 CFR 314.50 (j) Claimed Exclusivity.

The R.W. Johnson Pharmaceutical Institute is claiming marketing exclusivity under 21 CFR 314.108 (b)(2). We hereby certify, to the best of our knowledge, this drug has not previously been approved under section 505(b) of the act containing any active moiety in the drug for which we are seeking approval.

Should you have any questions and/or comments, please contact me directly at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director, Regulatory Affairs

1

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
920 Route 202, P.O. Box 300 Raritan, NJ 08869-0602

Fax Cover Sheet

Date:	November 8, 2001	**Pages:**	02
To:	Jennifer Mercier	**From:**	Karen Futterknecht
Dept.:	FDA	**Dept.:**	Regulatory Affairs
Fax #:	301-827-4267	**Fax #:**	908-722-5113
Telephone #:	301-827-4249	**Telephone #:**	908-704-4912

Comments: Dear Jennifer,
Attached is our request for marketing exclusivity.

Best regards,

Karen

ORIGINAL

Submission faxed Nov 1, 01 (Jan)

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

FDA OFFICIAL DOCUMENT

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to Request for CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. At this time we wish to provide additional CM&C information as requested by the CMC Reviewer in an email message dated 29 October 2001. This letter is formatted with the FDA request in **boldface** type followed by RWJPRI's response.

Chemistry, Manufacturing and Controls Information:

The Chemistry Reviewer's email stated, "I still need the items below to complete my review":

1. **Revised specification sheets for norelgestromin and ethinyl estradiol.**

The revised specification sheets for norelgestromin and ethinyl estradiol are provided behind the Attachment titled, "Revised Specifications/NGMN & EE".

2. **Test method and acceptance criteria for polyethylene terephthalate and** [redacted]

The requested test method and acceptance criteria were mailed to FDA on 30 October 2001, directly from [redacted], the supplier of the backing material, also faxed this information directly to FDA on 31 October 2001. This information was sent to the attention of Dr. Susan Allen at the DRUDP.

3. **The storage conditions on pouch, carton and packer tray labels should be changed as follows: "Store at controlled temperature at 25 C, excursion permitted to 15-30 C.**

RWJPRI agrees to revise the storage conditions as requested by FDA. We will however, change the word "excursion" to "excursions".

4. **The picture of the dancing woman on all labels provided in amendment dated 05 October 2001, should be removed.**

Although we acknowledge this request, RWJPRI believes that this logo should remain on the packaging components provided on 05 October 2001. Similar to other contraceptive and hormone replacement products on the market, we believe that the dancing woman is acceptable and does not warrant removal.

5. **The established name of the drug product, "norelgestromin/ethinyl estradiol transdermal system" on pouch and carton labels fin the amendment dated 05 October 2001, should be printed darker for ease of reading.**

RWJPRI agrees to print the requested text darker for ease of reading.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

cc: Desk copy to Dr. Amit Mitra, CM&C Reviewer HFD-580

REVIEWED
ACTION
LETTER
INITIAL
DATE

ORIGINAL

PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202 P.O. BOX 300 RARITAN, NJ 08869-0602

06 NOV 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

BC
NDA ORIG AMENDMENT

Amendment to a Pending Application:
Response to FDA Request For CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the Chemistry Reviewer's 02 November 2001 request to revise the storage conditions of the drug product. At this time we wish to amend the NDA with the following response. The FDA request appears below in bold face type and the RWJPRI response follows.

As per the stability guidance, please revise the storage conditions on the pouch, carton, and packer trays to add the equivalent degrees in Farenheit to the temperatures listed. The statement should read, *"Store at controlled temperature at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 ° F)."*

RWJPRI agrees to make the change to the storage conditions as described above to the packaging components. In addition, to remain consistent, the USPI will be revised in the same manner and submitted during label negotiations with the Agency.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

REVIEWS COMPLETED
CSO ACTION
LETTER
CSO INITIALS DATE

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist

APPEARS THIS WAY
ON ORIGINAL

FAXED 11/2/01 and 11/5/01 (vh)

THE R W JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

RECEIVED
NOV 0 7 2001
HFD-580
EVALUATION AND RESEARCH

02 NOV 2001

ORIG AMENDMENT

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 18 October 2001 email request. The FDA question appears below in bold face type and the RWJPRI response appears below it.

Question: Does the sponsor have any data information regarding the residual amount of drug content in the patches after use (7 days), or any data that indicates what % of the loaded drug is released from the patch on to the skin in 7 days (not just what is bioavailable)?

Response:

Tables 1-3 show the data requested by the reviewer. The data were generated by analyzing patches from human subjects for norelgestromin (NGMN) and ethinyl estradiol (EE), after the patches had been worn for 7 days. The apparent quantity of drug delivered (in % Formula Strength) was calculated by subtracting the quantity of drug remaining in the patch from the quantity in the control (unused patches). For study NRGEEP-PHI-003, the quantity of drug in the control patches was determined in a separate assay while for studies NRGEEP-PHI-004 and NRGEEP-PHI-005, the batch release assay values were used as the "control."

Tables 1-3 show the data available from the three studies cited above after 7 days of treatment. For studies NRGEEP-PHI-003 and -005, the patch was worn on the abdomen while for study NRGEEP-PHI-004, the patch was worn on different areas of the body (upper outer arm, abdomen, upper torso or buttock) as indicated in Table 2.

On examination of the data, it is clear that there is considerable variability in the data for apparent amounts of each drug delivered. For example, considering only the abdomen as the application site, the average apparent amounts of drug delivered (in the three studies) range from 164.6 to 276.9 μg/day for NGMN and from 29.9 to 42.9 μg/day for EE. When one includes the standard deviations, the range is 119.2 to 387.5 μg/day for NGMN and 19.1 to 60.9 μg/day for EE. Therefore, it is difficult to draw any firm conclusions on the true amount of drug delivered to the systemic circulation from these data. Our opinion is that the calculated apparent amount of drug delivered is, at best, a crude method of determining how much drug is actually delivered from the patch to the surface of the skin and does not reflect either the absolute dose delivered to the systemic circulation or the relative dose comparable to an oral contraceptive tablet.

At the time these determinations were done, they were being used as a development tool to help assess our progress in achieving the target quantities of actives in the patch and in the systemic circulation. They were not done in an attempt to achieve mass balance, which is a much more demanding and difficult exercise. For example, the skin was not swabbed and any residual adhesive collected to account for drug on the skin at the time the patch was removed. For these reasons, we are of the opinion that the data provided here represent estimates of the apparent amounts of delivered drug to the surface of the skin. and do not accurately reflect the quantity of each drug delivered into the circulation.

In the past, "difference" methods, which indirectly estimated the daily dose have been used. Doses were estimated, by difference, via subtraction of the residual amounts in the patch following removal after wear, from the amount of drug(s) present from unused patches, added to that extracted from the skin. Even with such precautions, such methods tend to be highly variable, and could lead to inaccurate estimations of the amount of drug delivered systemically. Such variability stems from the variability in patch extraction, skin extraction, and the large difference between what is actually in the patch and the small amount delivered per day.

The shortcomings of this approach were discussed with the agency on August 31, 1998 and, at the time, the more direct approach of determining the dose delivered to the systemic circulation (described in draft protocol of NRGEEP-PHI-014 submitted to the agency) was deemed acceptable. It was subsequently performed as study NRGEEP-PHI-014, a report of which was submitted in the NDA (Item 6/Item Volumes 2-3/Page1).

Table 1: Residual Drug Content Data From Study No. NRGEEP-PHI-003 [redacted] ot 00096) Following One Week of Wear on the Abdomen

Subject[a]	% Remaining (% FS)	
	Norelgestromin	Ethinyl estradiol
[redacted]	[redacted]	[redacted]
Mean (sd)	79.4 (±5.3)	70.3 (±10.1)
Control (6 unused samples)	NGMN (% FS)	EE (% FS)
Mean	98.6	98.2
	NGMN (% FS)	EE (% FS)
% "delivered" in 7 days	19.2 (±5.3)	27.9 (±10.1)
	NGMN (µg)	EE (µg)
Amount "delivered" per day	164.6* (±45.4)	29.9** (±10.8)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

* Sample calculation: 19.2 x 6000 µg/(100 x 7 days) = 164.6 µg/day

** Sample calculation: 27.9 x 750 µg/(100 x 7 days) = 29.9 µg/day

Table 2: Residual Drug Content Data From Study No. NRGEEP-PHI-004 (__ ot 00636) Following One Week of Wear

Subject[a]	% Remaining (% FS)							
	Norelgestromin				Ethinyl estradiol			
	Outer Arm	Abdomen	Torso	Buttock	Outer Arm	Abdomen	Torso	Buttock
[illegible]								
Mean (sd)	67.1 (±7.9)	65.6 (±12.9)	62.8 (±11.8)	65.2 (±8.4)	56.0 (±10.4)	55.4 (±16.8)	50.4 (±14.4)	52.9 (±13.5)
Control (Batch Release) Assay Result	NGMN (% FS) 97.9%				EE (% FS) 95.4%			
% "delivered" in 7 days	NGMN (% FS)				EE (% FS)			
	30.8 (±7.9)	32.3 (±12.9)	35.1 (±11.8)	32.7 (±8.4)	39.4 (±10.4)	40.0 (±16.8)	45.0 (±14.4)	42.5 (±13.5)
Amount "delivered" per day	NGMN (µg)				EE (µg)			
	264.0 (±67.7)	276.9 (±110.6)	300.9 (±101.2)	280.3 (±72.0)	42.2 (±11.2)	42.9 (±18.0)	48.2 (±15.4)	45.5 (±14.5)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.
[b] Patient 37 replaced Patient 21, who withdrew from the study.
ND = Not Determined

Table 3: Residual Drug Content Data From Study No. NRGEEP-PHI-005 (Lot 00636) Following One Week of Wear on the Abdomen

Subject[a]	% Remaining (% FS)	
	Norelgestromin	Ethinyl estradiol
Mean (sd)	68.2 (±5.8)	59.6 (±7.7)
Control (Batch Release)	NGMN (% FS)	EE (% FS)
Assay Result	97.9	95.4
	NGMN (% FS)	EE (% FS)
% "delivered" in 7 days	29.7 (±5.8)	35.8 (±7.7)
	NGMN (µg)	EE (µg)
Amount "delivered" per day	254.6 (±49.7)	38.4 (±8.2)

[a] The subject numbers as presented are internal code numbers which correspond to three digit subject numbers in the study report.

APPEARS THIS WAY
ON ORIGINAL

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to Dr. Dhruba J Chatterjee, FDA/DRUDP/HFD-580

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

SUBMISSION for eCTD

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NDA ORIG AMENDMENT N - 152

01 NOV 2001

Susan Allen, MD, Director
Division of Reproductive and Urologic
Drug Products HFD-580

Center for Drug Evaluation and Research
Food and Drug Administration
Attn.: Document Control Room 14B-04

5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

AMENDMENT TO A PENDING APPLICATION:
Labels/Labeling Information and Chemistry, Manufacturing & Controls Information

Dear Dr. Allen:

Reference is made to our pending NDA 21-180 for ORTHO EVRA™ and to the draft package components submitted with the original application on 20 December 2000 NDA (Item 2, Item Volume 1, Pages 52-59). Reference is also made to the draft packaging components that were amended to the pending application on 05 October 2001. At this time we would like to amend the NDA with a revised packaging component for the finished drug product replacement patch. A copy of the replacement patch overwrap and carton are included in this submission. This amendment is being provided at this time in order to gain a preliminary review of the text and text formatting planned.

Please note that these components were prepared prior to receiving Dr. Mitra's 29 October 2001 comments on the packaging components that were submitted to the Agency on 05 October 2001. Thus, as agreed, we will darken the text on the established name of the drug product, "norelgestromin/ethinyl estradiol transdermal system" on this replacement patch pouch and carton and revise the storage conditions to reflect, "store at controlled temperature at 25° C, excursions permitted to 15 - 30° C."

Labels/Labeling Information Enclosed:

- One black and white copy of the pouch overlabel to be applied to replacement pouches (quantity 1)
- One color copy of the replacement patch carton -Trade (quantity 1)

Chemistry, Manufacturing and Controls Information:

In addition, we would like to know if the CMC Reviewer has considered our 05 October and 12 October 2001 requests to include the two additional inactive

ingredients, "polyester backing film laminate" and "polyester release liner" on the cartons but not on the pouch labels. Due to space limitations, we are not able to add this additional text to the pouch labels without jeopardizing the readability of the pouch text.

Lastly, in the 24 October 2001 submission, RWJPRI agreed to change the drug product appearance specification upon approval, to include the following sentence, *"No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch."* We would like to know if the CMC Reviewer has reached a decision on our 24 October 2001 request to distribute, on approval, the batches that were manufactured prior to approval using the old appearance specification for the drug product.

If you have questions regarding this information please contact me at (908)-704-4812 or Valerie Donnelly at (908)-704-5891 or our dedicated number for FDA use (908)-704-4600.

Sincerely,

The RW Johnson Pharmaceutical Research Institute

Ramon Polo Ph.D.
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist

APPEARS THIS WAY
ON ORIGINAL

N [redacted]\tn\110101 package comp amend & cmc status.doc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

PHARMACEUTICAL R&D

ORIG AMENDMENT

30 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per the Biopharm Reviewer's requests received via email on 18 October 2001. The FDA question appears on the following pages in bold face type and the RWJPRI response appears after it. In addition, the last page of this submission contains a correction to the 12 October 2001 submission which contained responses to FDA's 27 September 2001, CM&C, Discipline Review Letter. We apologize for this error.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

REVIEWS COMPLETED

Send 1 Desk Copy to: Dr. Amit Mitra, Reviewing Chemist
FDA/DRUDP HFD-580
Rockville, MD 20857
Phone No: (301) 827-4260

N:\[redacted]ltr\103001 cmc-bioppharm response to fda req info.doc

ORIG AMENDMENT

29 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per the Medical Reviewer's request received via email on 19 October 2001 and as per Ms. Mercier's request on 09 August 2001 (response number 8 for Subject No. 1181). The FDA question appears below in bold face type and the RWJPRI response appears below it.

1. **Pregnancy outcomes for 15 on-therapy pregnancies and Subject 20018 (site 1025 in study 002).**

This information is provided in the Four-Month Safety Update submitted 12 April 2001. Another copy of this update can be provided if necessary.

2. **a. Site # for subject 21014 in study 002**
   b. Study, site#, subject# for subjects with the following SAEs:
   Depression
   Psychosis manic-depression
   Suicide attempt

See Attachment 1.

CSO INITIALS DATE

3. For each of the following parameter listed below, please provide the mean, median, range and

a. # of days per cycle of expected bleeding/spotting during the drug-free interval
b. # of days per cycle of unexpected bleeding/spotting during the 21 day drug
administration interval
c. total # of days of bleeding/spotting per cycle
d. duration of withdrawal bleeding (expected menses)

See Attachment 2.

4. a. give the % of subjects per cycle with ≥ 7 days of bleeding and/or spotting
b. give the % of subjects per cycle with > 10 days of bleeding and/or spotting

See Attachment 3.

5. a. per cycle, the % of subjects with amenorrhea (no withdrawal bleed during drug free interval)
b. per cycle, the % of subjects with amenorrhea for any 2 cycles (do not have to be consecutive)
c. per cycle, the % of subjects with amenorrhea for ≥ 3 cycles (do not have to be consecutive)

See Attachment 4.

6. a. % of subjects who reported at least 1 episode of breakthrough bleeding and/or spotting (BBT) at any time during the study
b. % of subjects with BBT in cycles 1-3
c. % of subjects with BBT in cycles 11-13

See Attachment 5.

7. Expected day of onset of withdrawal bleeding (menses) during drug free interval.

See Attachment 6.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-[illegible].

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Desk copy to : Dr. Daniel Davis
Medical Reviewer, DRUDP

APPEARS THIS WAY
ON ORIGINAL

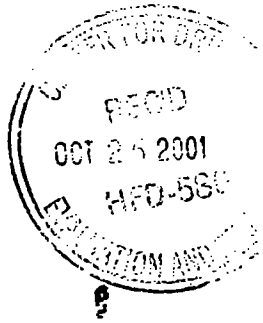
ORIGINAL ORIGINAL

25 OCT 2001

Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Products
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
Norelgestromin/Ethinyl Estradiol Transdermal System

NDA ORIG AMENDMENT



Amendment to a Pending Application:
Response to Request for Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180, submitted on 20 December 2000, for a norelgestromin/ethinyl estradiol transdermal system. Reference is also made to Ms. Mercier's 09 August 2001 telephone call to request information and to a letter sent to FDA 09 October 2001 stating that we were working to obtain this information. The request for additional information was as follows:

- For study CONT-003, Subject No. 1181, the hospital discharge summary is requested.

Attached is a copy of the hospital discharge summary for this subject.

If you have any questions concerning this submission please call me at (908) 704-4812, call Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

[redacted]
Director
Regulatory Affairs

Desk copy to: Dr. Daniel Davis,
Medical Reviewer, DRUDP

DFS / LOG
☐ LETTER
CSO INITIALS DATE

N:\[redacted]\LTR\102501discharge summary letter.doc/25 October 2001/JU

ORIGINAL

24 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the email requests from FDA received on 17 October 2001 and 19 October 2001. At this time, we are providing the information requested. The FDA request appears below in bold face type and the RWJPRI response appears below it.

17 October 2001 CM&C Request:

The appearance specification of the drug product should include the following additional sentence to address the cold flow: "No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch".

Response:

The Appearance specification will be changed to include the following sentence, "No change in surface area of the transdermal system should occur while removing the transdermal system from the pouch." This change will take effect upon approval and, as such, will apply to batches manufactured from that point forward. In the interim, we would like to request permission from the Agency to distribute, on approval, the batches that were manufactured with the old appearance specification.

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

n:\[redacted]\ltr\102401 response to fda req info.doc

19 October 2001 FDA Question:

In a submission you mention a "____ n facility in regards to the bioequivalence ... but this facility is not listed in the NDA ... me know what the intentions are regarding this facility?

Study NRGEEP-PHI-016 is a bioequivalence study and was conducted to evaluate a potential alternate manufacturer, _____ for ORTHO-EVRA. As the conclusion of this study is non-equivalence between ____ ORTHO-EVRA patch is not relevant to the current NDA submission. Additional bioequivalence studies with modified ___ process patch lots are being conducted under ___ subsequent to this NDA. Reports for these studies will be provided if necessary ___ will not be used as an alternate manufacturer for this product unless bioequivalence is achieved and then, only after obtaining approval from the agency.

The pharmacokinetic data from the ___ patch portion of Study NRGEEP-PHI-016 is from the NDA clinical lot 01607 and is relevant to the current NDA. In addition, these data from the ___ clinical lot are included with pharmacokinetic data from other Phase 1 studies in a pooled database from which population pharmacokinetic analyses were conducted and included in the current NDA.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

15 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)
ORIG AMENDMENT
BC

General Correspondence:
Response to FDA Request for CM&C Samples

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 submitted on 21 December 2000, for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system. At this time we wish to provide additional sample patches as per Dr. Amit Mitra's request to provide product that is either two years old or as close to the expiration date as possible.

Chemistry, Manufacturing and Controls Information:

Enclosed are 19 samples of the ORTHO EVRA™ transdermal contraceptive system. The patches are from lot number 00779 and the date of manufacture was 02 September 1999. This lot was made after the clinical trial lots and before the first PV lot, but underwent the same testing and QA scrutiny and batch record review as all of those lots. Please note that although these patches are not heat stamped with the trademark/dose, they do contain active ingredients and should be handled accordingly. For the purposes of this submission, the systems are sealed in a protective plastic bag.

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

Ramon Polo, PhD
Director
Regulatory Affairs

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

Desk Copy to: Dr. Amit Mitra, CM&C Reviewer HFD-580

N \[redacted]LTR\101501 2 yr patch samples .doc/15 October 2001/JU

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

12 OCT 2001

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For CM&C Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. Reference is also made to the Discipline Review Letter received on 27 September 2001. At this time we wish to provide the following responses. The FDA question appears below in bold face type and the RWJPRI response follows.

Drug Substance (norelgestromin)

1. **Please submit the information on the type of bag used during stability studies of norelgestromin.**

   a. [redacted]

   b. [redacted]

2. **Based on the ICH recommendations, the acceptance criteria for total impurities in the drug substance, norelgestromin should be tightened to [redacted] unless justified.**

   Based on data from batches of norelgestromin manufactured in the years 1999 to 2001, we accept the limit for total impurities in norelgestromin to "Not More [redacted] the supplier of this drug substance, will supply material that meets this specification.

   A copy of the revised norelgestromin drug substance specification will be sent to the Agency as soon as it is available.

3. **[redacted] is deficient. A deficiency letter was sent to the DMF holder.**

We are aware that a deficiency letter was sent to the DMF holder, however we believe the DMF number is actually [redacted] as noted in the Discipline Review Letter.

Drug Substance (ethinyl estradiol)

1. **The acceptance criteria for total impurity for ethinyl estradiol related substances should be tightened to [redacted] based on the analysis of the data provided, unless justified.**

The impurities and degradation products in drug substance batches of ethinyl estradiol (EE) are controlled by two chromatographic purity tests, [redacted]. Our acceptance criteria for [redacted] test are in conformance with that monograph.

Regarding the test [redacted]): we agree to tighten the total impurities specification from "Not More [redacted] to "Not More [redacted]. The justification for this level includes data that were included in the NDA but also additional data from a second supplier that are not included in this submission. The data were included in NDA 21-241 for ORTHO TRI-CYCLEN LO, Item 4A / Volume 1 / page 49. The second supplier is used for other Ortho-McNeil marketed products. Additional data from the second supplier are supplied in Attachment 1. This limit is consistent with the [redacted]

A copy of the revised drug substance specification will be submitted to the Agency as soon as it is available.

This information from [redacted] is presented in Attachment 2. Please note that information about molecular weight and % solids is not supplied to [redacted] by the vendor.

2. **Submit a certificate of analysis with coating weight and subsequent adhesion values, since those are parts of the specification.**

   A Certificate of Analysis from [redacted] showing the coating weight and subsequent adhesion values is included in Attachment 3.

3. **Provide labeling information of the jumbos and slit roll prior to shipping, and the storage conditions for the finished product.**

   Each liner roll is double-bagged and placed on pallets per the customer specification. The pallets are shrink wrapped. The packaged rolls are labeled with the product identity, lot number, quantity, manufacturer's name, and customer purchase order and part number. The rolls are stored in an air conditioned area until shipment.

   The liner rolls should be stored indoors, preferably in an air conditioned warehouse area at temperatures not exceeding 90 °F and relative humidity in the 20 – 70% range.

   Information on the packaging, labeling and storage is included at the end of the information provided in Attachment 2. A copy of a sample label roll and a sample packing slip for one pallet are provided in Attachment 4.

Non-woven backing film

1. **Provide test methods and acceptance criteria of polyethylene terephthalate and** [redacted]

   [redacted] purchases the polyethylene terephthalate and [redacted] which is located [redacted] to the [redacted] facility in [redacted] The polymer chip is transferred through pipelines, or sent via railcar from the [redacted] facility to the [redacted] facility. [redacted] receives this material based on Certificates of Analysis for each polymer

Number of Pages Redacted 5

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Confidential,
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3. **Provide a disposal procedure for the transdermal patch in the "How Supplied" section, since the drug product, when disposed, would contain a large quantity of the residual drugs and it may pose hazard by accidental use.**

   RWJPRI proposes to copy the disposal procedure text that currently appears in the patient labeling of the NDA into the How Supplied section of the physician labeling. The text is as follows and may be found in the original NDA, Item 2/Item Volume1/Page47: *"The used patch still contains some active hormones-throw it away by carefully folding it in half so that it sticks to itself."*

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson Pharmaceutical Research Institute

Ramon Polo, PhD
Director
Regulatory Affairs

Send 1 desk copy to: Dr. Amit Mitra, FDA/DRUDP/HFD-580, Reviewing Chemist

APPEARS THIS WAY ON ORIGINAL

11 OCT 2001

ORIG AMENDMENT

Dr. Susan Allen, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III, (HFD-580)
Division of Reproductive and Urologic Drug Product
Attn.: Document Control Room 14B-04
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Rockville, Maryland 20857-1706

NDA 21-180
ORTHO EVRA™
(norelgestromin/ethinyl estradiol transdermal system)

General Correspondence:
Response to FDA Request For Information

Dear Dr. Allen:

Reference is made to pending New Drug Application (NDA) 21-180 for ORTHO EVRA™, a norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal contraceptive system, submitted on 20 December 2000. We are providing information at this time as per Dr. Chatterjee's 05 October 2001 email request. The FDA question appears below in bold face type and the RW... response appears below it.

Question:
I am reviewing the dissolution information provided my section (6) of the NDA. The lot/batch #s used for these pieces of information are 01107 (———); 01517 ——— and 01607 ———. Was wondering whether the sponsor could confirm that these lots were identical to the phase 3 and the to-be-marketed lots.

Response:
Lots 01107, 01517 and 01607, were indeed the Phase 3 lots. The to-be-marketed lots meet NDA specifications that were developed by a procedure that included these three Phase 3 lots as well as other lots (for details, please see Section 3.6.3 of the NDA [Item 4/Item Volume 4/Page 24]). We believe this meets the reviewer's

Should you have any questions and/or comments, please contact me at (908) 704-4812, contact Valerie Donnelly at (908) 704-5891 or call our telephone line dedicated for FDA use at (908) 704-4600.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE