CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

Trade Name: Ortho-Cyclen 0.25mg/0.035mg

Ortho Tri-Cyclen 0.18mg/0.035mg, 0.215mg/0.035mg, 0.25mg/0.035mg

Generic Name: norgestimate/ethinyl estradiol tablets

Sponsor: Johnson RW

Approval Date: 10/20/1999

Indications: Ortho-Cyclen & Ortho Tri-Cyclen: For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Ortho Tri-Cyclen: For the treatment of moderate acne vulgaris in females, greater than or equal to 15 years of age, who have no known contradictions to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

APPROVAL LETTER

NDA 19-697/S-015
NDA 19-653/S-020

OCT 20 1999

R.W. Johnson Pharmaceutical Research Institute
Attention: Donna M. Panasewicz
Director, Regulatory Affairs
U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Panasewicz:

Please refer to your supplemental new drug applications dated September 26, 1997, received September 27, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ortho Tri-Cyclen Tablets, and Ortho-Cyclen Tablets.

We acknowledge receipt of your submissions dated April 29, 1999 and September 23, 1999. Your submission of April 29, 1999 constituted a complete response to our January 5, 1998 action letter.

These supplemental new drug applications provide for the establishment of an interim release and stability dissolution specification of Q=80% at 30 minutes for both norgestimate and ethinyl estradiol in the 250 µg norgestimate/35µg ethinyl estradiol strength tablets.

We also refer to the October 18, 1999, telephone conversation between you and Dr. David Lin of this Division, in which you agreed to accept the proposed dissolution specification of Q=80% at 30 minutes for the 250 µg norgestimate/35 µg ethinyl estradiol tablets as an interim specification. This specification will be re-evaluated in one year, at which time the you have agreed to submit additional data to explain the noted difference in dissolution behavior between the 180 µg and 215 µg norgestimate containing tablets, as compared to the 250 µg norgestimate containing tablets.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely, 10/19/99

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

NDA 19-697/S-015
NDA 19-653/S-020

cc:
Archival NDAs 19-697, 19-653
HFD-580/Div. Files
HFD-580/J.Mercier
HFD-580/Rhee/Lin
HFD-095/DDMS-IMT
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JM/October 19, 1999
Initialed by: Colangelo10.19.99/Lin10.19.99/Rhee10.19.99/Rarick10.19.99
final: October 19, 1999
filename: 19653S20.WPD

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

NON-APPROVABLE LETTER

ORIGINAL

NDA 19-653/S-020
NDA 19-697/S-015

The R.W. Johnson Pharmaceutical Research Institution
Attention: Ms. Donna Panasewicz
Manager, Regulatory Affairs
920 Route 202 South,
P.O. Box 300
Raritan, NJ 08869-0602

JAN 05 1998

Dear Ms. Panasewicz:

Please refer to your supplemental new drug application dated September 26, 1997, received September 29, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

Ortho-Cyclen (norgestimate and ethinyl estradiol) Tablets, NDA 19-653; and
Ortho-TriCyclen (norgestimate and ethinyl estradiol) Tablets, NDA 19-697.

The User Fee goal date for these applications is March 29, 1998.

We have completed our review and find the information presented is inadequate, and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies/reasons may be summarized as follows:

1. There is a definite trend in which batches of 250 μg norgestimate (NGM)/35 μg ethinyl estradiol (EE) strength tablets are passing S1 dissolution testing. [ ]

2. It appears that the [ ] of the pregelatinized starch has an effect on the dissolution of norgestimate. If the [ ] of the pregelatinized starch has a large effect on the dissolution of norgestimate, the variable needs to be controlled.

3. Please explain why there was a significantly lower percentage of S1 dissolution failures in the batches of 215 μg NGM/35 μg EE strength tablets and 180 μg NGM/35 μg EE strength tablets.

4. There is a higher percentage of S1 testing batch failures with the 250 μg NGM/35 μg EE tablets manufactured at the [ ] [ ] This would suggest that failure of the batches is not only simply due to the variation in [ ] of the pregelatinized starch excipient used in manufacturing, but also due to process control variations in manufacturing.

5. The firm's conclusion from their analysis suggests that [ ] Therefore, the firm needs to assess whether these process variables have a greater effect on norgestimate dissolution than the [ ] of the pregelatinized starch.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental applications. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

1/5/98

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

cc:
Orig. NDA
HFD-580
HFD-820/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-580/DLin/MRhee
HFD-580/CKish/12.22.97/n19653na.s20
concurrence:LPauls 12.30.97/DLin 1.5.98/MRhee 1.5.98

SUPPLEMENT NOT APPROVABLE (S/NA)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

CHEMISTRY REVIEW(S)

ORIGINAL

DEC 23 1997

CHEMIST'S REVIEW

1. Organization
DRUDP HFD-580

2. NDA Number
19-697

3. Name and Address of Applicant
R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

4. Supplement
SCS 015
9/26/97

5. Name of Drug
Ortho Tri-Cyclen

6. Nonproprietary Name
Norgestimate/ethinyl estradiol (NGM/EE)

7 Supplement Provides For
Information to establish a final release and interim stability dissolution specification of Q=80% at 30 minutes for both norgestimate and ethinyl estradiol.

8. Amendment

9. Pharmacological Category
Contraception

10. How Dispensed
RX

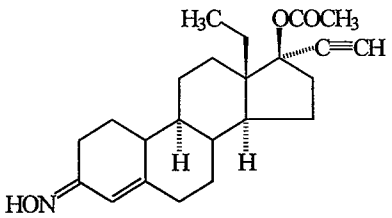
11. Related
NDA 19-653, S-020

12. Dosage form
Tablets

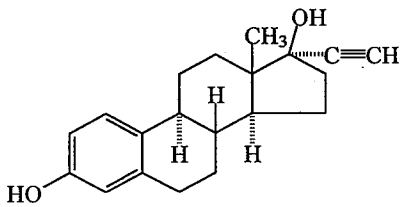
13. Potency
250 μg /35 μg NGM/EE, 215 μg /35 μg NGM/EE, 180 μg /35 μg NGM/EE

14. Chemical Name and Structure

1) Norgestimate: a) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate
b) 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)



2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)



15. Comments
This supplement was submitted for approval of a final dissolution specification at time of release for both norgestimate and ethinyl estradiol of Q=80% at 30 minutes, and an interim stability dissolution specification of Q=80% at 30 minutes. Reference is made to a supplement (S-013) dated June 28, 1996 which provided for an interim specification for dissolution of Q=80% at 20 minutes using 0.05% TWEEN 20 as the dissolution

medium. The firm committed to collecting dissolution data at the 15 minute and 20 minute intervals for one year, and continue investigation into the low dissolution results obtained for norgestimate on Batches 16A632 - 16D639 and supply an explanation in one year. This supplement contains the following information:

Appendix I: Requested dissolution data with proposed dissolution specification
Appendix II: Investigation of the norgestimate dissolution

See Chemist's Review of S-013 for more background information.

16. Conclusion and Recommendation

Based on the data and explanations by the firm, this supplement is not approvable. See review notes for comments.

17. Name	**Reviewer's Signature**	**Date**
David T. Lin, Ph.D. Review Chemist		12-18-97

cc:
Orig. NDA #19-697
HFD-580/Division File
HFD-580/CKish
HFD-580/MRhee/DLin

R/D Init by: MJ Rhee 12/23/97

filename: S19697.015 (doc)

3 Page(s) Withheld

Chemistry Review #1 (19-697/S-015)

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CHEMIST REVIEW #2
OF **SUPPLEMENT**

OCT 18 1999

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 19-697/SCS-015
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 26-SEP-1997
   Stampdate: 27-SEP-1997
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate: 29-APR-1999, 23-SEP-1999
   Stampdate: 30-APR-1999, 24-SEP-1999
5. **RECEIVED BY CHEMIST:** 05-MAY-1999

6. **APPLICANT NAME AND ADDRESS:**
   R.W. Johnson Pharmaceutical Research Institute
   920 Route 202 South
   P.O. Box 300
   Raritan, NJ 08869-0602

7. **NAME OF DRUG:**
   Ortho Tri-Cyclen Tablets

8. **NONPROPRIETARY NAME:**
   Norgestimate/ethinyl estradiol

9. **CHEMICAL NAME/STRUCTURE:**
   1) Norgestimate: a) (+)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate
      b) 18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)
      see USP for structure

   2) Ethinyl estradiol: a) 19-Nor-17α-pregn-1,3,5(10)-trien-20-yne-3,17-diol
      b) 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)
      see USP for structure

10. **DOSAGE FORM(S):**
    Tablet

11. **POTENCY:**
    250/35 μg, 215/35 μg, and 180/35 μg norgestimate/ethinyl estradiol

12. **PHARMACOLOGICAL CATEGORY:**
    Progestin, estrogen/Contraception

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    None

16. SUPPLEMENT PROVIDES FOR:

Information to establish a final release and interim stability dissolution specification of Q=80% at 30 minutes for both norgestimate and ethinyl estradiol.

17. COMMENTS

The April 29, 1999 amendment is a response to the January 5, 1998 FDA not approvable letter.

The September 23, 1999 amendment is a commitment to provide additional data one year after approval of this supplement that may explain the difference in dissolution behavior between the 180 µg and 215 µg norgestimate containing tablets, and the 250 µg norgestimate containing tablets.

During a teleconference on October 18, 1999 with Donna Panasewicz of The R.W. Johnson PRI, an agreement was reached that the sponsor would use the proposed dissolution specification as an interim specification (see attached teleconference memo).

18. CONCLUSIONS AND RECOMMENDATIONS:

This Prior Approval Supplement may be approved. **Issue an approval letter with the following statement: "The proposed dissolution specification of Q=80% at 30 minutes for the 250 µg norgestimate/35 µg ethinyl estradiol tablets is acceptable as an interim specification. This specification will be re-evaluated in one year at which time the sponsor has agreed to submit additional data to explain the noted difference in dissolution behavior between the 180 µg and 215 µg norgestimate containing tablets, and the 250 µg norgestimate containing tablets."**

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist	10/18/99	18-OCT-1999

cc: Original: NDA 19-697/SCS-015
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

INIT by MJ Rhee 10/18/99

Filename: S19697AC.015 (doc)

2 Page(s) Withheld

Chemistry Review #2 (19-697/S-015)

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-020 & 19-697/S-015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Memorandum

To: NDA 19-653/SCS-020, Ortho-Cyclen Tablets (norgestimate/ethinyl estradiol)

NDA 19-697/SCS-015, Ortho Tri-Cyclen Tablets (norgestimate/ethinyl estradiol)

Through:

From: David Lin, Ph.D. 10/18/99

Date: October 18, 1999

Re: Teleconference with Donna Panasewicz of The R.W. Johnson PRI to discuss Dissolution Specifications

---

A call was made to Donna Panasewicz, Director Regulatory Affairs, in which I asked whether the proposed dissolution specification of Q=80% at 30 minutes for the 250 µg norgestimate/35 µg ethinyl estradiol tablets would be acceptable as an **interim** specification. This specification would be re-evaluated, one year after approval of the supplements, when additional data to support the dissolution specification will be submitted by the sponsor for review. Since the sponsor will not be submitting an amendment agreeing to their acceptance of this interim specification, this provision will be added to the approval letter.

cc:
Orig. NDA #19-653/SCS-020 and NDA # 19-697/SCS-015
HFD-580/Division File
HFD-580/JMercier
HFD-580/MRhee/DLin

Filename: S19653Tcon.020 (doc)

ORIGINAL
NDA SUPP AMEND
SCS-015 BC

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

SEP 23 1999

Dr. Lisa Rarick
US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

NDA 19-653 (S-020)
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please cross-refer to:

NDA 19-697 (S-015)
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Amendment to Supplements S-015 and S-020

Dear Dr. Rarick:

Reference is made to our approved New Drug Applications for ORTHO-CYCLEN Tablets NDA 19-653, and ORTHO TRI-CYCLEN Tablets NDA 19-697, our norgestimate/ethinyl estradiol containing oral contraceptive products and, specifically, to our submission dated 29 April 1999 which responded to the Agency's questions of 08 January 1998 and requested a revised dissolution specification, Q=80% in 30 minutes, for our 250µg norgestimate/35µg ethinyl estradiol tablets.

Reference is also made to a telephone conversation on 20 September 1999 with Dr. David Lin of your Division and Ms. Donna Panasewicz of The R.W. Johnson Pharmaceutical Research Institute, wherein Dr. Lin requested that we commit in writing to provide any additional information that may be available which may help to explain the difference in dissolution behavior between our 180µg and 215µg norgestimate containing tablets and our 250µg norgestimate containing tablets.

At this time we commit to provide whatever information is available which may help to explain the above noted difference in dissolution behavior one year after approval of these supplements.

A field copy of this submission is being forwarded directly to the FDA [ ] District office and [ ] District Office. We certify that the field copy is a true copy of the information contained in the archival and review copies of this supplemental application.

Should you have any questions, you may contact me directly at (908) 218-6140 or at our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Donna M. Panasewicz
Director
Regulatory Affairs

Attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

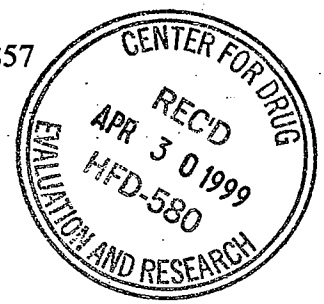
NDA SUPP AMEND

S-015-BC

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

APR 29 1999

Dr. Lisa Rarick
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857



NDA 19-653 (S-020)
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please cross-refer to:

NDA 19-697 (S-015)
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Response to FDA Comments
Request for Expedited Review

Dear Dr. Rarick:

Reference is made to our approved New Drug Application for ORTHO-CYCLEN Tablets NDA 19-653, and ORTHO TRI-CYCLEN Tablets NDA 19-697, our norgestimate/ethinyl estradiol containing oral contraceptive products. Further reference is made to the subject supplemental new drug applications dated 26 September 1997 (copy attached) which provided for a final dissolution specification at time of release for both norgestimate and ethinyl estradiol of Q=80% at 30 minutes and an interim stability dissolution specification of Q=80% at 30 minutes. Reference is further made to the comments provided in your letter of 5 January 1998 (copy attached) regarding these supplemental applications and our letter dated 8 January 1998 (copy attached) in which we advised the Agency of our intent to amend the supplemental NDAs.

Attached are our responses to the above referenced comments presented in a **Comment and Response format** that primarily addresses the norgestimate dissolution assay results. This focus is necessary as norgestimate is a poorly soluble drug substance versus the ethinyl estradiol component and as such is inherently subject to greater variability.

1. **COMMENT:**

- **There is a definite trend in which batches of 250 μg norgestimate (NGM)/35 μg ethinyl estradiol (EE) strength tablets are passing S1 dissolution testing.** [ ]

RESPONSE:

Please refer to Attachment 1 for plots of 20 minute norgestimate dissolution data for batches of ORTHO-CYCLEN and ORTHO TRI-CYCLEN manufactured [ ] since the dissolution medium was changed to an aqueous 0.05% Tween 20 solution. Plots of 30-minute norgestimate dissolution assay data are presented as a reference benchmark to our previous submission.

During this time, neither the Raw Material Specifications nor the Manufacturing Process have been modified from those approved in the original NDA. The norgestimate dissolution assay data presented herein demonstrate that:

1. The Process is not changing at either site.
2. The Process is equivalent at each site.

In addition, the above referenced data clearly illustrate that the norgestimate dissolution assay results for the tablets produced at each plant are equivalent. This assessment is supported by statistical treatment of the data as reported in Attachment 2.

Based upon our review and interpretation of the above information, the "trends" referred to in Comment 1 are representative of normal process variability.

2. **COMMENT:**

It appears that the [ ] of the pregelatinized starch has an effect on the dissolution of norgestimate. If the [ ] of the pregelatinized starch has a large effect on the dissolution of norgestimate, the variable needs to be controlled.

RESPONSE:

Further analysis of the data from a total of 130 batches shows that there is no significant correlation between starch [ ] and dissolution. Therefore, this line of inquiry was terminated. See details in Attachment 3.

3. **COMMENT:**

Please explain why there was a significantly lower percentage of S1 dissolution failures in the batches of 215 μg NGM/35 μg EE strength tablets and 180 μg NGM/35 μg EE strength tablets.

RESPONSE:

Attachment 1 shows 20-minute dissolution data for all 3 strengths of norgestimate-containing contraceptive tablets manufactured [ ] The average dissolution assay values expressed as a percent of label claim decrease as the tablet strength increases. Therefore, it is expected that the highest strength tablets will have the greatest percentage of S1 failures, and that the lowest strength tablets will have the fewest S1 failures.

The mean of the average dissolution assay values minus 2 standard deviations is about 89% for 180 µg tablets, 85% for 215 µg tablets, and 77% for 250 µg tablets. This, when expressed as µg norgestimate dissolved, corresponds to mean dissolution rates of:

8.0 µg/min for the 180 µg norgestimate product
9.1 µg/min for the 215 µg norgestimate product
9.6 µg/min for the 250 µg norgestimate product

The above more accurately reflects the dissolution data for both ORTHO-CYCLEN and ORTHO TRI-CYCLEN Tablets than when reported as percent label claim dissolved. The highest strength is not really dissoluting more slowly. The norgestimate drug substance is seen to be releasing from all three at essentially the same rate. Given the similarity of the formulations this is expected.

In other words, although the rates are equivalent for the different norgestimate strengths, there is insufficient time for the highest strength norgestimate to dissolve.

It should also be emphasized that for the 250 µg strength, the dissolution assay specification of Q = 80% at 20 minutes is within 2 standard deviations of the process average. **Under these conditions, [ ]% of all 250 µg product batches fail at the S1 level of testing and [ ]% of the batches fail at the S2 level.** Thus, a product failing the dissolution specification of Q = 80% at 20 minutes is not of use as an indicator of process control, because it does not signal that a batch fails because of a 'Special Cause'.

4. **COMMENT:**

There is a higher percentage of S1 testing batch failures with the 250 µg NGM/35 µg EE tablets manufactured at the [ ] This would suggest that failure of the batches is not only simply due to the variation in [ ] of the pregelatinized starch excipient used in manufacturing, but also due to process control variation in manufacturing.

RESPONSE:

As discussed in response to Questions 1 and 3, the dissolution characteristics of tablets from the two sites are the same. Over any short time period, there may be differences in the percentage of S2 testing, but this is NOT indicative of a difference in process control.

5. **COMMENT:**

The firm's conclusion from their analysis suggests that [ ]

Therefore, the firm needs to assess whether these process variables have greater effect on norgestimate dissolution than the [ ] of the pregelatinized starch.

RESPONSE:

The data presented above indicate that the norgestimate dissolution differences between strengths disappear when the data are converted to µg instead of percent label claim. Therefore, attempting further control of the factors cited in the September 1997 report is not called for. The appropriate approach is to change the dissolution specification to one that is consistent with the process control parameters.

Our investigations of the manufacturing process for ORTHO-CYCLEN and ORTHO TRI-CYCLEN products have been on-going since the receipt of the 5 January 1998 Agency correspondence. The resultant findings, summarized below, were used to address the above comments.

A. There are intrinsic differences in the norgestimate dissolution rate of the three strengths of tablets when the tablets are tested according to the current dissolution method and the results are expressed in terms of percent label claim dissolved.

   However, when the dissolution rate is expressed in terms of µg norgestimate dissolved, the three strengths behave essentially the same. This is what would be expected for tablets whose only important difference is the quantity of the very poorly soluble drug substance. Therefore, the "slower" dissolution of the 250 µg product is an artifact of the way the result is expressed.

B. Both manufacturing sites are producing equivalent product, evidence of a reliable and well-controlled process.

C. Historically, from a QA/QC manufacturing control theory perspective, a process is taken to be under control when the monitored parameter is within the range of 2 to 3 standard deviations of the mean.

At this time, the approved dissolution specification for all norgestimate products is Q = 80% at 20 minutes. This is within 2 standard deviations from the mean of the 250 µg product. **Under these conditions, [ ]% of all 250 µg product batches fail at the S1 level of testing and /% of the batches fail at the S2 level.** Thus, a product failing the dissolution specification of Q = 80% at 20 minutes is not of use as an indicator of process control, because it does not signal that a batch fails because of a 'Special Cause'.

Both from control theory and our experience, it is our belief that the Q = 80% at 20 minutes specification is inappropriate for the 250 µg product.

D. Controlling the variables in processing or the normal variability in raw materials when these are common to all strengths, as they are in this case, cannot be expected to erase the differences in dissolution rate expressed as percent label claim.

The only formulation and process differences among the strengths are: (a) the ratio of norgestimate to the other tablet ingredients, (b) the presence of colorant and (c) the concentration of norgestimate in the [ ] solution used in the [ ] process. To change dissolution would require significant changes in formula or process, which we do not believe is called for in a product that has a history of safety and efficacy.

Our understanding based on previous communications is that the FDA desires dissolution methods and specifications that signal when a process is out of control. The current method and specifications when applied to the 250 µg product do not comply with the FDA's intent.

RECOMMENDATION:

We propose the following norgestimate dissolution specifications for product release and stability based upon statistical analysis of the historical data (Attachment 4) and the desires of the FDA for a discriminating dissolution methodology to signal when a process is out of control:

250 µg : **Q = 80% at 30 minutes** using the current dissolution medium and conditions (0.05% Tween 20, USP Apparatus 2 at 75 rpm). This is the same specification that was proposed in the 26 September 1997 submission.

215 µg: Retain **Q = 80% at 20 minutes.**

180 µg: Retain **Q = 80% at 20 minutes.**

The proposed **ethinyl estradiol specifications** are the same as for norgestimate:

250 µg: **Q = 80% at 30 minutes.**
215 µg: **Q = 80% at 20 minutes.**
180 µg: **Q = 80% at 20 minutes.**

We believe that the above information serves to clarify our submission of 26 September 1997, addresses issues raised in the 5 January 1998 FDA response and proposes a substantive norgestimate dissolution assay specification for ORTHO-CYCLEN Tablets based upon established Process Control Theory principles.

We trust that we have adequately addressed all of the Agency's questions of 5 January 1998 and that the data presented in this submission substantiates the appropriateness of the above requested specification.

As the current specification is and has been a substantial burden for our Company with regard to repeat testing, we respectfully request that this submission be given "Expedited Review". I will follow up with the Agency approximately two weeks after your receipt of this submission to discuss the contents of this submission and discuss if a formal meeting with Agency representatives is necessary to obtain closure.

A field copy of this submission is being forwarded directly to the FDA [ ] District Office and [ ] District Office. We certify that the field copy is a true copy of the information contained in the archival and review copies of this supplemental application.

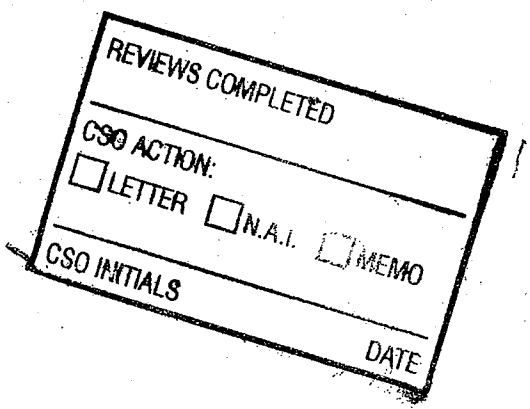
Should you have any questions, you may contact me directly at (908) 218-6140 or at our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Donna M. Panasewicz
Director
Regulatory Affairs

Attachments



ORIGINAL

noted DTC 1/14/98

noted 1/12/98 RB

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

NDA SUPP AMEND
SCS-015
SNC

JAN - 8 1998

Lisa Rarick, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II, HFD 580
Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

NDA 19-653 - (S-020)
ORTHO-CYCLEN® Tablets
(Norgestimate/Ethinyl Estradiol)

Please cross-refer to:

noted Prahalad 1/14/98

NDA 19-697 - (S-015)
ORTHO TRI-CYCLEN® Tablets
(Norgestimate/Ethinyl Estradiol)

INTENT TO AMEND SUPPLEMENTS

Dear Dr. Rarick:

Reference is made to our supplemental new drug applications dated September 26, 1997 for ORTHO-CYCLEN Tablets (S-020) NDA 19-653 and for ORTHO TRI-CYCLEN Tablets (S-015) NDA 19-697 which provided for a final dissolution specification at time of release for both norgestimate and ethinyl estradiol of Q=80% at 30 minutes and an interim stability dissolution specification of Q=80% at 30 minutes. Reference is further made to a January 5, 1998 letter from the Agency (copy attached) in which we were advised that the information presented in our applications is inadequate and the supplemental applications are not approvable.

In accordance with 21 CFR 314.120, we wish to notify you of our intent to file an amendment to each of the supplemental NDAs referred to above to support approval of these applications.

Should you have any questions, you may contact me directly at (908) 218-6140 or at our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

NA 1/14/98

Donna M. Panasewicz
Manager
Regulatory Affairs

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-697/S-015

OCT - 8 1997

The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Attention: Donna Panasewicz
Manager, Regulatory Affairs

Dear Ms Panasewicz:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ORTHO TRI-CYCLEN Tablets (Norgestimate/Ethinyl Estradiol)

NDA Number: 19-697

Supplement Number: S-015

Date of Supplement: September 26, 1997

Date of Receipt: September 29, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 28, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-697/S-015
HFD-580/Div. Files
HFD-580/CSO/

SUPPLEMENT ACKNOWLEDGEMENT

mailed 10/16/97 pk3

ORIGINAL

NDA NO. 19-697 REF. NO. 015
NDA SUPPL FOR S015

Reviewed 1/6/98 DTL

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

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS 10 DATE 1/5/98

CENTER FOR DRUG REC'D SEP 29 1997 HFD-510 EVALUATION AND RESEARCH

SEP 26 1997

Lisa Rarick, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
HFD 580
Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

CENTER FOR DRUG REC'D SEP 30 1997 HFD-580 EVALUATION AND RESEARCH

NDA 19-653
ORTHO-CYCLEN® Tablets
(Norgestimate/Ethinyl Estradiol)

Please cross-refer to:

NDA 19-697
ORTHO TRI-CYCLEN® Tablets
(Norgestimate/Ethinyl Estradiol)

noted KDalegre 1/8/98

SUPPLEMENTAL APPLICATION

Dear Dr. Rarick:

Reference is made to our approved New Drug Applications, NDA 19-653 for ORTHO CYCLEN Tablets and NDA 19-697 for ORTHO TRI-CYCLEN Tablets, our norgestimate/ethinyl estradiol containing products.

Further reference is made to our supplemental applications (S-018 and S-013 respectively) dated June 28, 1996 which provided for an interim specification for dissolution of Q=80% at 20 minutes utilizing 0.05% TWEEN 20 as the dissolution medium. In the June 28 supplement, we committed to the following:

1. To collect dissolution data at the 15 minute interval, in addition to the 20 minute interval, for one year for informational purposes.

2. Continue our investigation into the low dissolution results obtained for norgestimate on Batches 16A632 through 16D639 and supply the Agency with an explanation of the low results in one year.

3. Accept an interim specification of Q=80% at 20 minutes using 0.05% TWEEN 20 for one year.

At this time we are submitting a supplemental application to provide the information which we had committed to and to establish both a final release and interim stability dissolution specification.

We wish to note that in addition to testing at the required 15 and 20 minute time points, we elected to also test at a 30 minute time point during this one year period. Dissolution results at all three time points, along with the S1 failure rates and a statistical analysis, are presented in this supplement.

Also of particular interest is that as an outcome of our investigation we have been able to identify that the [ ] size in the excipient starch substantially contributes to the fluctuations in the dissolution results obtained, particularly at the 15 and 20 minute time points.

Based upon the above and the information contained in this supplement, we are requesting approval for the following:

1. A final dissolution specification at time of release for both norgestimate and ethinyl estradiol of Q=80% at 30 minutes.
2. An interim stability dissolution specification of Q=80% at 30 minutes.

Justification for the selection of the 30 minute testing interval is as follows:

- The fluctuation in the dissolution results caused by the variation in starch [ ] size plateaus at 30 minutes.
- It is the appropriate testing interval to identify possible Quality Control issues.
- It eases the burden of re-testing and investigating fluctuations in the dissolution results caused by starch.

We trust that we have satisfied the commitments made to the Agency and that the information contained in this supplement is supportive of our proposal for the above dissolution specifications.

A field copy of this submission is being forwarded directly to the FDA [ ] District Office and [ ] District Office. We certify that the field copy is a true copy of the information contained in the archival and review copies of this supplemental application.

Should you have any questions, you may contact me directly at (908) 218-6140 or at our phone number dedicated for FDA use at (908) 704-4600.

Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

Donna M. Panasewicz
Manager
Regulatory Affairs