

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-806**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 21-806

SUPPL #

HFD # 590

Trade Name N/A

Generic Name Metronidazole Vaginal Gel, 0.75%

Applicant Name TEVA Pharmaceuticals

Approval Date, If Known May 20, 2005

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

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

YES

NO

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

The study conducted is a bioequivalence study with clinical endpoints which was intended to fulfill the Office of Generic Drug's requirement for the determination of bioequivalence of TEVA's proposed drug product to the referenced list drug, MetroGel-Vaginal, 0.75% (NDA 20-208). However, the study results fell outside the range of 80-120 % required to demonstrate clinical bioequivalence. Therefore, the application submitted under 505(j) was refused to be received by OGD and subsequently, TEVA filed its drug product under 505(b)(2) as NDA 21-806.

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA# 20-208 MetroGel-Vaginal, 0.75%

NDA# 19-737 Metrogel Topical, 0.75%  
20-901 MetroLotion, 0.75%  
20-53 MetroCream

NDA# 18-353 Flagyl IV

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

to PART II, Question 1 or 2 was "yes."

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

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the

effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

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

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

Investigation #1  
IND # YES  ! NO   
! Explain:

Investigation #2  
IND # YES  ! NO   
! Explain:

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

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

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

YES  NO

If yes, explain:

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Name of person completing form: Yon Yu, Pharm D.

Title: Regulatory Project Manager

Date: May 19, 2005

Name of Office/Division Director signing form: Renata Albrecht, M.D.

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

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Renata Albrecht  
5/20/05 01:05:10 PM  
NDA 21806

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-806 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: July 20, 2004 Action Date: May 20, 2005

HFD-590

Trade and generic names/dosage form: Metronidazole Vaginal Gel, 0.75%

Applicant: TEVA Pharmaceuticals Therapeutic Class: Antibacterial

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of bacterial vaginosis (formerly referred to as *Haemophilus* vaginitis, *Gardnerella* vaginitis, nonspecific vaginitis, *Corynebacterium* vaginitis, or anaerobic vaginosis) in non-pregnant women

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study. (Bacterial Vaginosis is not a disease that occurs in pre-menarchal females; thus, a pediatric study in this population is not warranted. The safety and effectiveness of Metronidazole Vaginal Gel, 0/75% demonstrated in adult females with bacterial vaginosis can be extrapolated to post-menarchal adolescent females.)

There are safety concerns.

Other:

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population

- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA             
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

NDA [REDACTED]  
Page 3

(revised 12-22-03)

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/s/

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Yon C. Yu  
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Withheld Track Number: Administrative-1



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 28, 2005

<b>To:</b> Mr. Vincent Andolina	<b>From:</b> Yon Yu, Pharm D. Regulatory Project Manager
<b>Company:</b> TEVA Pharmaceuticals	Division of Division of Special Pathogen and Immunologic Drug Products
<b>Fax number:</b> (215) 591-8812	<b>Fax number:</b> (301) 827-2475
<b>Phone number:</b> (215) 591-8642	<b>Phone number:</b> (301) 827-2195
<b>Subject:</b> NDA 21-806 CMC Information Request	

**Total no. of pages including cover:** 3 (including the cover page)

**Comments:** If you have any questions, please contact Yon Yu at 301-827-2195.

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**Document to be mailed:** YES  NO

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ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL,  
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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2127. Thank you.

Please provide response to the following CMC comments.

1. Please include the viscosity test (analytical procedure and acceptance criteria) as part of the drug product specification.
2. Please include (or provide a commitment to develop) an analytical procedure (HPLC) and acceptance criteria for impurities in the metronidazole drug substance specification.

3. Please provide a description of the drug product manufacturing process depicting all steps and conditions, including the in-process controls. Identify all critical process steps and operating conditions.
4. Please provide the results of the applicator dosage evaluation studies demonstrating that the applicator consistently delivers a dose of five gram of the [REDACTED]. Also, provide results of the extraction studies conducted on the proposed drug product container/closure system.
5. Please describe the color of the gel, the procedure used to determine it and how it changes on storage. Please explain any changes in color. Please note that description acceptance criterion "Clear to yellow" is not appropriate and should be revised.
6. Please provide data from the weight loss testing for the product packaged in commercial tubes and include the weight loss test in the drug product specification (both release and stability).
7. Please note that the acceptance criteria for methylparaben or propylparaben assays in the regulatory (stability) specification for the drug product proposed as ""Not less than [REDACTED] and not more than [REDACTED]" do not appear justified. Please revise (narrow) them.
8. Please verify if the stability testing results described as [REDACTED] indicate the testing results of samples taken from different areas of the individual tube.
9. Please provide updated stability data for the primary stability batches of the drug product. Also, please provide the results of freeze/thaw testing.

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/s/

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Yon C. Yu  
2/28/05 09:50:42 AM  
CSO



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

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE: December 1, 2004**

<b>To:</b> Mr. Vincent Andolina Director, Regulatory Affairs Liquids, Semisolids and Specialty Projects	<b>From:</b> Yon Yu, Pharm D. Regulatory Project Manager
<b>Company:</b> TEVA Pharmaceuticals, USA	Division of Division of Special Pathogen and Immunologic Drug Products
<b>Fax number:</b> (215) 591-8812	<b>Fax number:</b> (301) 827-2325
<b>Phone number:</b> (215) 591-8642	<b>Phone number:</b> (301) 827-2195
<b>Subject:</b> NDA 21-806	

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**Total no. of pages including cover:** 3

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**Comments:**

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**Document to be mailed:** YES  NO

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Please refer to your new drug application dated July 19, 2004, received July 20, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Vaginal Gel, 0.75%.

The following are clinical and statistical comments on NDA 21-806.

1. Please note the modified Intent-to-Treat (mITT) population should include all randomized patients who receive at least one dose of study drug and who have bacteriologic evidence of bacterial vaginosis (i.e., Nugent score  $\geq 4$ ) at baseline. No post-baseline factor(s) should result in exclusion from the mITT population. Subjects who have missing data should be considered failures in the mITT analysis.
2. Please populate the attached table, accounting for all subjects excluded from each of the three analysis populations. We have added some of the numbers for you. Your current definitions of the Safety (Intent-to-Treat) and PP populations are acceptable; however, please indicate the reason for exclusion from the PP population in the attached table. Only the primary reason for exclusion should be indicated for each subject. Rank ordering of the reasons for exclusion should follow the order of appearance in the table.
3. Clinical non-inferiority in the Office of New Drugs is assessed using a 95% confidence interval about the difference in therapeutic cure rates (primary efficacy endpoint) between the test drug and comparator for both the mITT and PP populations. Please recalculate your results for the primary efficacy analysis using a 95% confidence interval. Similarly, a 95% confidence interval should be calculated for the secondary efficacy endpoints for both the mITT and PP populations.

#### Subject Evaluability

	Metronidazole Vaginal Gel, 0.75%	MetroGel® Vaginal Gel, 0.75%
<b>Number Randomized</b>	<b>293</b>	<b>286</b>
<b>Number Included in the Safety Population*</b>	<b>220</b>	<b>239</b>
Subjects who did not take any study medication or did not return for any post-baseline visit	73	47
<b>Number Included in the Modified Intent-to-Treat (MITT) Population**</b>	<b>216</b>	<b>232</b>
<i>Reasons for Exclusion from the MITT Population</i>		
Did not meet the bacteriological definition of BV at baseline (Nugent score < 4)	4	7
<b>Number Included in the Per Protocol (PP) Population</b>	<b>155</b>	<b>159</b>
<i>Reasons for Exclusion from the PP Population</i>		
Subjects with known or suspected infectious causes of vulvovaginitis other than BV (e.g., candidiasis, <i>Trichomonas vaginalis</i> , <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , active herpes simplex, or human papilloma virus)		
Started using study medication later than 2 days after Visit 1		
Had sexual intercourse /used intra-vaginal products during the first 7 days of the study		
Received less than 3 consecutive days of therapy or more than 6 days of therapy		
Use of prohibited medication (list number of subjects by category of drug i.e., systemic antimicrobials, systemic corticosteroids, warfarin, etc.)		
Other exclusion criteria violation (list specific example)		
Lost to follow-up		
Test-of-Cure visit (Visit 3) outside the window		

\* subjects taking at least one dose to study medication

If you have any questions regarding above comments or would like to have a further discussion, please contact Yon Yu, Pharm D., Regulatory Project Manager, at (301) 827-2195.

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/s/

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Yon C. Yu  
12/1/04 10:55:36 AM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-806

TEVA Pharmaceuticals USA

Attention: Vincent Andolina

Director, Regulatory Affairs, Liquid's, Semi-Solids, and Specialty Projects

1090 Horsham Road

P.O. Box 1090

North Wales, PA 19454

Dear Mr. Andolina:

Please refer to your July 19, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Vaginal Gel, 0.75%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on September 19, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

- The safety of the concentration of hypromellose [REDACTED] in the proposed formulation.

We are providing the above comment to give you preliminary notice of a potential review issue. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. The study reports for the comparative clinical efficacy study in PDF format, including the associated tables.
2. Data sets as SAS transport files.
3. Results of the comparative physico-chemical testing (i.e. viscosity, pH, specific gravity, etc.) for the reference listed drug (MetroGel-Vaginal, 0.75%) and Teva's product (Metronidazole Gel, Vaginal, 0.75%) conducted using the same method and testing conditions.

NDA 21-806

Page 2

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Yon Yu, Pharm D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and  
Immunologic Drug Products  
Office Drug Evaluation IV  
Office New Drugs

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/s/

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Renata Albrecht  
9/15/04 04:15:40 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-806

TEVA Pharmaceuticals USA  
Attention: Vincent Andolina  
Director, Regulatory Affairs, Liquid's, Semi-Solids, and Specialty Projects  
1090 Horsham Road  
P.O. Box 1090  
North Wales, PA 19454

Dear Mr. Andolina:

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

Name of Drug Product:	Metronidazole Vaginal Gel, 0.75%
Review Priority Classification:	Standard (S)
Date of Application:	July 19, 2004
Date of Receipt:	July 20, 2004
Our Reference Number:	NDA 21-806

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 18, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 20, 2005.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Special Pathogen and Immunologic Drug Products, HFD-590  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-806

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Special Pathogen and Immunologic Drug Products, HFD-590

Attention: Document Room

9201 Corporate Blvd

Rockville, Maryland 20850

If you have any questions, call Yon Yu, Pharm D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

*(See appended electronic signature page)*

Ellen F. Molinaro, R.Ph.

Chief, Project Management Staff

Division of Special Pathogen and

Immunologic Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

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/s/

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Ellen Molinaro  
9/10/04 12:40:33 PM  
NDA 21-806



Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index?  YES NO

• Was form 356h included with an authorized signature?  YES NO  
**If foreign applicant, both the applicant and the U.S. agent must sign.**

• Submission complete as required under 21 CFR 314.50?  YES NO  
 If no, explain:

• If an electronic NDA, does it follow the Guidance?  N/A YES  
 NO

**If an electronic NDA, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• If in Common Technical Document format, does it follow the guidance?  N/A YES NO

• Is it an electronic CTD?  N/A YES NO  
**If an electronic CTD, all certifications must be in paper and require a signature.**

Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information submitted on form FDA 3542a?  YES NO

• Exclusivity requested? YES, \_\_\_\_\_ years  NO  
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature?  YES NO  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

**NOTE:** Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,  
 “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge . . . .”

• Financial Disclosure forms included with authorized signature?  YES  NO  
 (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

• Field Copy Certification (that it is a true copy of the CMC technical section)?  YES  NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

• PDUFA and Action Goal dates correct in COMIS?  YES  NO  
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

• Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

• List referenced IND numbers:

• End-of-Phase 2 Meeting(s)?  N/A Date(s) \_\_\_\_\_  NO  
 If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)?  N/A Date(s) \_\_\_\_\_  NO  
 If yes, distribute minutes before filing meeting.

\*\* The sponsor developed its product with the intention of filing it under 505(j) and the application was initially submitted under 505(j). However, OGD issued a Refuse to Receive letter since the bioequivalence study results fell outside the range of 80-120 % required to demonstrate clinical bioequivalence. \*\*

**Project Management**

• All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  N/A YES  NO

• Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS?  N/A YES  NO

• MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS?  N/A YES  NO

• If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?  N/A YES  NO

**If Rx-to-OTC Switch application:**

• OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?  N/A YES  NO

• Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

• If a controlled substance, has a consult been sent to the Controlled Substance Staff?  N/A YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment?  YES      NO
- If no, did applicant submit a complete environmental assessment? YES      NO
- If EA submitted, consulted to Nancy Sager (HFD-357)? YES      NO
  
- Establishment Evaluation Request (EER) submitted to DMPQ?  YES      NO
  
- If a parenteral product, consulted to Microbiology Team (HFD-805)?  N/A    YES      NO

**If 505(b)(2) application, complete the following section:**

- Name of listed drug(s) and NDA/ANDA # MetroGel-Vaginal, 0.75% NDA 20-208
  
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

NDA 21-806 is the same as the RLD (MetroGel-Vaginal, 0.75%) in its indication, active ingredient, dosage form, route of administration, and dosing regimen. The application was refused to be received under 505(j) since OGD’s review found the proposed drug product not to be bioequivalent to the RLD. In its clinical endpoint BE study, the proposed drug product demonstrated a slight improvement over the RLD. Subsequent to receiving the NDA submission and prior to the NDA filing, OGD was consulted to explore the possibility of 505(j) route for this drug product. OGD confirmed that the product cannot be received as an ANDA.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES       NO
  
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES       NO
  
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES       NO
  
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

X  21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

<u>Patent #s</u>	<u>Expiration Date</u>
# 4837378	June 6, 2006
# 5536743	July 16, 2013
# 5840744	January 15, 2008

\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_ 21 CFR 314.50(i)(1)(ii): No relevant patents.

\_\_\_ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

\_\_\_ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES  NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES  NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A  YES  NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES  NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER  
The number of the applicant's IND under which the studies essential to approval were conducted.

IND # \_\_\_\_\_ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

**Appears This Way  
On Original**

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: September 10, 2004

**BACKGROUND:**

NDA 21-806 came to DSPIDP as a result of Teva receiving Refuse to Receive letters from OGD (RTR letters dated 21-Oct-02 and 27-Jan-03). This product is the same as the RLD (MetroGel-Vaginal, 0.75% (NDA 20-208)) in its indication, active ingredient, dosage form, route of administration, and dosing regimen. The application was developed with the intention of being filed under 505(j). However, OGD issued a Refuse to Receive letter since the bioequivalence study results fell outside the range of 80-120 % required to demonstrate clinical bioequivalence. Subsequent to receiving the NDA submission and prior to the NDA filing, OGD was consulted to explore the possibility of 505(j) route for this drug product. OGD confirmed that the product cannot be received as an ANDA.

**ATTENDEES:**

**ASSIGNED REVIEWERS:**

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Meyer
Secondary Medical:	
Statistical:	Dixon
Pharmacology:	McMaster
Chemistry:	Matecka
Environmental Assessment (if needed):	
Biopharmaceutical:	Gieser
Microbiology, sterility:	Suvarna
Microbiology, clinical (for antimicrobial products only):	
DSI:	N/A
Regulatory Project Management:	Yu
Other Consults:	OGD (Hixon/Scardina)

Per reviewers, are all parts in English or English translation?  YES  NO

If no, explain:

CLINICAL FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES  NO
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_  NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?  N/A YES NO

CLINICAL MICROBIOLOGY      NA \_\_\_\_\_ FILE   X        REFUSE TO FILE \_\_\_\_\_

STATISTICS      FILE   X        REFUSE TO FILE \_\_\_\_\_

BIOPHARMACEUTICS      FILE   X        REFUSE TO FILE \_\_\_\_\_

- Biopharm. inspection needed:      YES       NO

PHARMACOLOGY      NA \_\_\_\_\_ FILE   X        REFUSE TO FILE \_\_\_\_\_

- GLP inspection needed:      YES       NO

CHEMISTRY      FILE   X        REFUSE TO FILE \_\_\_\_\_

- Establishment(s) ready for inspection?       YES      NO
- Microbiology      YES      NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

  X   The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

  X   No filing issues have been identified.

\_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

\_\_\_\_\_  
Regulatory Project Manager, HFD-590

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)?  YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

MetroGel-Vaginal, 0.75% NDA 20-208

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?  YES  NO  
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

*NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This product is the same as the RLD (MetroGel Vaginal, 0.75% (NDA 20-208)) in its indication, active ingredient, dosage form, route of administration, and dosing regimen. The application was refused to be received under 505(j) since OGD's review found the proposed drug product not to be bioequivalent to the RLD. In its clinical endpoint BE study, the proposed drug product demonstrated a slight improvement over the RLD. Subsequent to receiving the NDA submission and prior to the NDA filing, OGD was consulted to explore the possibility of 505(j) route for this drug product. OGD confirmed that the product cannot be received as an ANDA.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under YES  NO

21 CFR 314.101(d)(9).

10. Are there certifications for each of the patents listed for the listed drug(s)?  YES  NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

<u>Patent #s</u>	<u>Expiration Date</u>
# 4837378	June 6, 2006
# 5536743	July 16, 2013
# 5840744	January 15, 2008

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Written statement from patent owner that it consents to an immediate effective date upon

approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  

YES                      NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  

YES                       NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  

N/A                       YES                      NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv)).?  

N/A                      YES                      NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  

YES                      NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  

YES                      NO
- EITHER  
The number of the applicant's IND under which the studies essential to approval were conducted.  

IND # \_\_\_\_\_                      NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?  

YES                      NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES                      NO

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

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Yon C. Yu  
5/5/05 02:49:21 PM  
CSO