

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205223Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 205223

SUPPL # 000

HFD #

Trade Name n/a

Generic Name Metronidazole vaginal gel 1.3%

Applicant Name Valeant Pharmaceuticals North America LLC

Approval Date, If Known

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?

505(b)(1)

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

d) Did the applicant request exclusivity?

YES NO

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

Three years

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

YES NO

NDA 205223 (metronidazole vaginal gel 1.3%)

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

YES NO

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's for topical/vaginal metronidazole (MetroGel-Vaginal 20208, Vandazole 21806, Noritate 20743, Metrogel 19737 and 21789)

NDA's for oral use (Flagyl 12623 and 20334, Protostat 18871, Metronidazole 18764, Flagyl ER 20868)

NDA's for IV use (Flagyl 18353, Metro IV 18674, Metronidazole 18890)

Several ANDAs for oral and intravenous use

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

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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

Investigation #3 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

Investigation #3 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"):

1. An Open-label Study of the Pharmacokinetics of Metronidazole Vaginal Gel, 1.3%
2. A Multicenter Randomized, Investigator-Blinded, Phase 2, Dose-Ranging Study of Metronidazole Vaginal Gel in the Treatment of Bacterial Vaginosis

3. Phase 3, Multicenter, Randomized, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of Product 55394 in the Treatment of Bacterial Vaginosis

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 # 107484 YES !
! NO
! Explain:

Investigation #2
IND # 107484 YES !
! NO
! Explain:

Investigation #3
IND # 107484 YES !
! NO

(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
! NO
Explain: ! Explain:

Investigation #2
YES
! NO
Explain: ! Explain:

Investigation #3
YES !
! NO

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Explain:

! 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:

=====

Name of person completing form: Jane A. Dean, RN, MSN
Title: Regulatory Health Project Manager
Date: 2/5/14

Name of Office/Division Director signing form: Katherine Laessig, MD
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JANE A DEAN
03/20/2014

KATHERINE A LAESSIG
03/20/2014

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

NDA#: 205223

PRODUCT PROPRIETARY NAME: N/A

ESTABLISHED/GENERIC NAME: Metronidazole gel 1.3%

APPLICANT/SPONSOR: Valeant Pharmaceuticals

PROPOSED INDICATION/S:

(1) Treatment of bacterial vaginosis in non-pregnant women

(2) _____

(3) _____

(4) _____

NDA STAMP DATE: May 24, 2013

PDUFA GOAL DATE: March 24, 2014

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER: SN 000

Does this application provide for:

NEW *active ingredient(s) (includes new combination);* *indication(s);* *dosage form;* *dosing regimen; or* *route of administration?*

New dosing regimen

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Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication?

No

Is this application in response to a PREA (Postmarketing Requirement) PMR? No

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.

Pediatric Patients who have not yet experienced menarche

Reason(s) for waiving pediatric assessment requirements

Studies are impossible or highly impractical: the number of pediatric patients is so small; the incidence and prevalence of BV in females who have not reached menarche is negligible

3. *Provide justification for Waiver:*

The very low incidence and prevalence of bacterial vaginosis in pre-menarchal females makes it impracticable to perform clinical studies.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

In section 8.4 of labeling, the sponsor proposes the following statement: (b) (4)

The division is not in agreement with this statement and proposes the following: Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

DEFERRAL REQUEST

The applicant has not submitted a formal deferral request at this time; however, they submitted a proposal for deferred study (see below).

Please attach:

Pediatric Record

1. **Age groups included in the deferral request:** (b) (4)
2. **Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

A waiver is requested for pre-menarcheal females.

3. **Reason/s for requesting deferral of pediatric studies in pediatric patients with disease:**

a. Adult studies are completed and ready for approval.

4. **Provide projected date for the submission of the pediatric assessment (deferral date):** Not submitted

5. **Did applicant provide certification of grounds for deferring assessments?** Yes

Applicant had proposed (b) (4) The Division disagreed and requested that the applicant submit a proposed study to evaluate the safety of metronidazole gel 1.3% in the adolescent population. The applicant submitted a study proposal by email on November 21, 2013.

6. **Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?** Yes No

SPONSOR'S PROPOSED PEDIATRIC PLAN

Formatted Table

1. **Has a pediatric plan been submitted to the Agency?** Yes

2. Does the division agree with the sponsor's plan? No

Applicant had requested that [REDACTED] (b) (4). The Division disagreed and requested that the sponsor submit a proposed study to evaluate the safety of metronidazole gel 1.3% in the adolescent population. The sponsor submitted a study proposal by email on November 21, 2013.

The sponsor proposes a [REDACTED] (b) (4)

3. **Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?** No

- a. **Protocol Submission:** Protocol synopsis was submitted as an email attachment on November 21, 2013
- b. **Study Completion:**
- c. **Study Submission:**

4. **Has a Written Request been issued?** No

5. **Has a PPSR been submitted?** No

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Types of Studies/Study Design:

Study to evaluate the safety and efficacy of metronidazole vaginal gel 1.3% in post-menarchal females < 18 years of age

Nonclinical Studies:

None

Clinical Studies:

The Division agrees with the clinical study proposed by the applicant: a comparative study comparing metronidazole vaginal gel 1.3% to vehicle gel.

Age group and population (indication) in which study will be performed:

Non pregnant post-menarcheal females < 18 years of age

Number of patients to be studied or power of study to be achieved:

Approximately 30-50 patients who receive the active drug.

Entry criteria:

Non pregnant females with bacterial vaginosis diagnosed according to Amsel criteria (abnormal vaginal discharge, positive whiff test, vaginal pH >4.5, and $\geq 20\%$ clue cells on a saline wet mount) with a Nugent score >4

Clinical endpoints:

Clinical cure, defined as return of physiologic discharge on Day 7

Timing of assessments:

Screening and Day 7 study visits

Statistical information (statistical analyses of the data to be performed):

Descriptive statistics

Clinical cure and frequency of adverse events in subjects receiving the active drug or vehicle gel will be compared. Statistical analysis

will be descriptive.

Division comments on product safety:

Are there any safety concerns currently being assessed? **No**

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? **No**

Will a DSMB be required? **No**

Division comments on product efficacy:

In adults, single administration of metronidazole gel 1.3% was superior to placebo for clinical cure in non-pregnant women at least 18 years of age on Days 7 and 21 post-therapy. For other topical products approved for the treatment of BV, such as metronidazole gel 0.75% and clindamycin cream 2%, the Division had previously extrapolated efficacy and safety from the adult population to the adolescent population.

Division comments on sponsor proposal to satisfy PREA:

The sponsor submitted a waiver request for pre-menarcheal females. The Division agrees with the waiver request for this population because the incidence and prevalence of BV in pre-menarcheal females renders studies unfeasible.

The sponsor submitted a protocol synopsis of a comparative study in post-menarcheal females < 18 years of age. The Division agrees with the proposal to defer studies in this population. However, the sponsor has not yet proposed dates for initiation of this study. The product has been evaluated in adults and the NDA is currently being reviewed, with PDUFA due date March 24, 2014.

Of note, metronidazole vaginal gel 0.75% is approved for the treatment of BV in adults. The product labeling states that safety and effectiveness in children have not been established. The active moiety, metronidazole, is also marketed as an oral tablet, oral capsule, extended release oral tablet, topical skin lotion and as an IV formulation.

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1.9 Pediatric Administrative Information

4. Proposed Pediatric Study Request and Amendments

(b) (4)



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

/s/

JANE A DEAN
11/21/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205223	NDA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: n/a Established/Proper Name: Metronidazole Gel 1.3% Dosage Form: Vaginal Gel		Applicant: Valeant Pharmaceuticals North America LLC Agent for Applicant (if applicable):
RPM: Jane A. Dean, RN, MSN		Division: Division of Anti-Infective Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is March 24, 2014 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action and date: Approval AP, 3/24/14
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	X
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	X
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	N/A
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 7/26/13 <input type="checkbox"/> DMEPA 1/15/14 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/20/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 12/24/13 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	RPM Filing Review and Memo of Meeting 7/26/13 RPM Labeling Review 7/26/13 <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12/4/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	X
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 8/25/10
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	n/a
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	2/12/14
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	3/24/14
PMR/PMC Development Templates (<i>indicate total number</i>)	1
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	1/15/14
• Clinical review(s) (<i>indicate date for each review</i>)	1/15/14
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 11, Clinical Review 1/15/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	1/7/14
Clinical Microbiology Review(s) (indicate date for each review)	1/7/14
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	1/21/14
Statistical Review(s) (indicate date for each review)	1/21/14
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	1/16/14
Clinical Pharmacology review(s) (indicate date for each review)	1/16/14
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	1/7/14
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	1/7/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	2/5/14
• Branch Chief/Team Leader Review(s) (indicate date for each review)	2/4/14
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	2/4/14, 3/21/14
❖ Microbiology Reviews	<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	CMC Review, 2/5/14, Pg. 51
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 2/4/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

JANE A DEAN
03/24/2014

**PeRC PREA Subcommittee Meeting Minutes
December 4, 2013**

PeRC Members Attending:

Lynne Yao
 Rosemary Addy
 Hari Cheryl Sachs
 George Greeley
 Robert “Skip” Nelson
 Jane Inglese
 Barb Buch
 Wiley Chambers
 Tom Smith
 Karen Davis-Bruno
 Greg Reaman ((b) (4) , Metronidazole (b) (4) reviews only)
 Daiva Shetty
 Shrikant Pagay
 Ruthanna Davi
 Lily Mulugeta
 Dianne Murphy
 Peter Starke
 Ruthianna Davi
 Shrikant Pagay
 Suan McCune
 William J. Rodriguez

PREA

	(b) (4)			
10:20	NDA	205223	Metronidazole Partial Waiver/Deferral/Plan	Treatment of bacterial vaginosis non-pregnant women
10:40	(b) (4)			
	(b) (4)			

Metronidazole Partial Waiver/Deferral/Plan

- NDA 205223 seeks approval for Metronidazole for the treatment of bacterial vaginosis non-pregnant women.
- This application has a PDUFA goal date of March 24, 2014.
- The application triggers PREA as a new dosing regimen.
- *PeRC Recommendations:*
 - The PeRC agreed with the Division to grant a partial waiver in patients less than 12 years of age because studies would be impossible or highly impractical. The PeRC noted that the “standard age” used to define patients who are post-menarchal for other products (e.g., oral contraceptive products) is 12 years of age and above. The deferral would include patients 12 to 17 years because the product is ready for approval in adults.

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/s/

GEORGE E GREELEY
12/17/2013

From: Dean, Jane
To: [Michael O"Beirne - C \(mobeirne@medicis.com\)](mailto:mobeirne@medicis.com)
Cc: [Diane Stroehmann \(dstroehmann@medicis.com\)](mailto:dstroehmann@medicis.com)
Subject: NDA 205223 (metronidazole gel 1.3%) - information request
Date: Friday, November 08, 2013 11:49:00 AM
Importance: High

Michael, we have the following information request. Please note the short turnaround time we are asking for.

[NDA 205223, metronidazole gel 1.3% for the treatment of BV](#)

Your proposed pediatric development plan indicates that you intend to request a waiver of pediatric studies for pre-menarchal females (b) (4)

[REDACTED]
[REDACTED]
[REDACTED] our current thinking is that safety and efficacy should be evaluated in this patient population.

Please provide a study proposal to evaluate the safety and tolerability of metronidazole vaginal gel 1.3% in post-menarchal females < 18 years of age. Please submit your proposal within the next 14 days.

Jane A. Dean, RN, MSN
Project Manager
DAIP/OAP/OND
Bdg. 22, Rm. 6397
Office: 301-796-1202
Fax: 301-796-9881
Email: jane.dean@fda.hhs.gov

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/s/

JANE A DEAN
11/08/2013



NDA 205223

INFORMATION REQUEST

Valeant Pharmaceuticals North America LLC
Attention: Michael O'Beirne
Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Mr. O'Beirne:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Vaginal Gel 1.3%

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by November 20, 2013, in order to continue our evaluation of your NDA.

1. It is stated in Section P.2.3 that particle size is monitored by the drug substance manufacturer. Please update the drug substance specification in S.4.1 with particle size acceptance criteria.
2. In Section S.4.4 (Batch Analyses), the impurities are reported as "Pass", instead of actual values. Please update the batch analysis results with actual impurity values and provide representative chromatograms for the drug substance impurity analysis.
3. It is stated that the [REDACTED] (b) (4) [REDACTED] are critical quality attributes as they impact the homogeneity and quality of the drug product. However, some process parameters, which have potentials to impact product quality, were missing from P.3.3 and P.3.4. Please include [REDACTED] (b) (4) [REDACTED]
4. The proposed acceptance criteria for viscosity is too wide compared to the observed viscosity ranges both at release and during stability studies for the clinical and registration batches. There is no data to demonstrate that the drug product at the proposed lower and upper viscosity limits [REDACTED] (b) (4) cp) have appropriate clinical applicability and

processability. Please tighten the viscosity acceptance criteria based on the viscosity results of clinical batches and manufacturing capability.

5. Please include the test for uniformity of dosage units in the drug product specification (USP <905>) or justify by an appropriate in-process control [REDACTED] (b) (4) [REDACTED].
6. Please provide an assessment indicating that total [REDACTED] (b) (4) in the drug product meet the requirement [REDACTED] (b) (4) of the application.
7. Since the concentration of the drug substance in metronidazole vaginal gel (1.3%) is close to its solubility (1.57%) in the formulation, please provide the solubility data at 5°C or add “Do Not Put in Refrigerator” in the Labeling to prevent precipitation during storage.
8. Please report stability results for “Total Impurities”, since they were not found in the stability data in P.8.3.
9. Please provide representative original chromatograms of the drug product spiked with impurities [REDACTED] (b) (4) obtained at DPT using HPLC methods [REDACTED] (b) (4) and [REDACTED] (b) (4), respectively.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURAWA
11/04/2013



NDA 205223

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Valeant Pharmaceuticals
Attention: Diane Stroehman, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehman:

Please refer to your New Drug Application (NDA) dated May 24, 2013, received May 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Metronidazole Vaginal Gel 1.3%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is March 24, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 24, 2014.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

Chemistry, Manufacturing and Control

1. Provide results of dose delivery studies using at least 10 pre-filled applicators to demonstrate that the proposed vaginal applicator is capable of delivering a consistent 5 gram dose of the proposed drug product, metronidazole vaginal gel, 1.3%.

2. As indicated in the formulation development section, the formulation is designed (b) (4)

Please answer
the following questions for clarification:

(b) (4)

4. Provide 2 drug product samples in the commercial packaging configuration.

We are providing the above comments to give you preliminary notice of potential review issues. 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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond to the above requests for information by August 16, 2013. 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.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Adverse Reactions

1. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

We request that you resubmit labeling that addresses these issues by August 16, 2013. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Anti-Infective Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JANE A DEAN
08/01/2013

SUMATHI NAMBIAR
08/01/2013



NDA 205223

NDA ACKNOWLEDGMENT

Valeant Pharmaceuticals North America LLC
Attention: Diane Stroehmann, MSRA, RAC
Executive Director, Regulatory Affairs
7720 North Dobson Road
Scottsdale, AZ 85256

Dear Ms. Stroehmann:

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

Name of Drug Product: Metronidazole Gel 1.3%

Date of Application: May 24, 2013

Date of Receipt: May 24, 2013

Our Reference Number: NDA 205223

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 July 23, 2013 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

FRANCES V LESANE
06/07/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107,484

Graceway Pharmaceuticals, LLC
Attention: Sean Brennan, Ph.D.
Sr. Vice President, Regulatory Affairs
340 Martin Luther King Jr. Blvd., Suite 500
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Metronidazole Vaginal Gel, 1.3%.

We also refer to the meeting between representatives of your firm and the FDA on August 25, 2010. The purpose of the End of Phase 2 meeting to discuss the results of your Phase 2 clinical study and discuss your proposed Phase 3 clinical program.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jacquelyn Smith, M.A., Regulatory Health Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Eileen Navarro Almario, M.D.
Acting Deputy Director
Division of Special Pathogen and Transplant
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
Presentation (Handouts)

IND 107,484

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: IND
Meeting Date August 25, 2010
Application Number: 107,484
Product Name: Metronidazole Vaginal Cream, 1.3%
Indication: Bacterial Vaginosis
Sponsor Name: Graceway Pharmaceuticals
Meeting Chair: Eileen Navarro Almario, M.D.
Meeting Recorder: Jacquelyn Smith, M.A.

FDA ATTENDEES

Division of Special Pathogen and Transplant Products (DSPTP)

Renata Albrecht, M.D., Director

Eileen Almario Navarro, M.D., Acting Deputy Director

Lin Qi, Ph.D., Chemistry Reviewer OPS, ONDQA, DNDQAII

Rapti Madurawe, Ph.D., Chemistry Pharmaceutical Assessment Lead, OPS, ONDQA,
DNDQAII

William Taylor, Ph.D., Pharmacology/Toxicology Supervisor

Owen McMaster, Ph.D., Pharmacology/Toxicology Reviewer

Hala Shamsuddin, M.D., Medical Officer

Shukal Bala, Ph.D., Microbiology Team Leader

Lynette Berkeley, Ph.D., Microbiology Reviewer

Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology Team Leader, OTS, OCP,
DCP4

Yoriko Harigaya, Ph.D., Clinical Pharmacology Reviewer, OTS OCP, DCP4

Karen Higgins, Sc.D., Statistics Team Leader, OTS, OB, DBIV

Cheryl Dixon, Ph.D., Statistics Reviewer, OTS, OB, DBIV

Jacquelyn Smith, M.A, Regulatory Health Project Manager

SPONSOR ATTENDEES

Graceway Pharmaceuticals

John Bellamy, J.D., Executive Vice President and General Counsel
Michael Nordsiek, Executive Vice President, Product Development
Sean Brennan, PhD., Senior Vice President, Regulatory Affairs
Sharon Levy, M.D., Senior Vice President, Clinical Research
James Lee, MD Ph.D., Chief Medical Officer
Jason Wu, M.D., Executive Director, Clinical Research
James Kulp, Senior Director, Clinical Research
Robert Babilon, Senior Director Product Development

Consultants

(b) (4), Biostatistics Consultant
(b) (4), Clinical Pharmacology Consultant
(b) (4), Clinical Consultant
(b) (4), Consulting Toxicologist

BACKGROUND

The purpose of the August 25, 2010 End-of Phase 2 meeting was to discuss the results of the sponsor's Phase 2 clinical study and discuss their proposed Phase 3 clinical program. On July 23, 2010 Graceway Pharmaceuticals, LLC submitted a briefing package containing background information and proposals to support the face to face meeting with FDA. On August 23, 2010, FDA sent their preliminary meeting comments and detailed responses to guide the discussion. On August 25, 2010 Graceway Pharmaceuticals, LLC requested additional clarifications with comments to the FDA meeting preliminary communication during the face to face meeting.

DISCUSSION

The meeting began with introductions of attendees, and an introduction of the company, Graceway Pharmaceuticals, and the various products managed by the company. Graceway stated that the FDA comments to the questions, posed in their briefing package, were detailed and clear, but they had few additional clarifications.

For **Chemistry** questions, no further clarifications were requested of the Agency. Graceway stated that the dose to be used in Phase 3 trial and the proposed marketed product will be 5-grams, in the same dose volume that was studied in the Phase 2 study, and dispensed in a pre-filled applicator which was described in the briefing package submitted July 23, 2010.

For **Pharmacology Toxicology**, no further clarifications were requested, and Graceway stated that nonclinical topics would be addressed at a preNDA meeting, and within the submission of a marketing application.

For **Clinical Pharmacology**, Graceway sought clarification as to whether the inclusion of an analysis for systemic levels of the hydroxymetabolite could be considered optional.

- FDA responded that analysis of the hydroxymetabolite would be useful, but is not required.
- FDA confirmed that their understanding of the expected outcome from this PK study in volunteers would be the systemic levels of metronidazole and any tolerability information.
- Graceway proposed to remove the 0.75% metronidazole arm from the pharmacokinetic study, such that the study would be a 1-arm, open-label, single dose study of the 1.3% product in healthy volunteers. FDA agreed that a 1-arm, PK study of only the 1.3% product would be acceptable to support the NDA application.

For **Clinical/Biostatistics**, Graceway presented an alternative Phase 3 study design, one that was in agreement with the Agency's suggestion for a placebo-controlled study (**see attachment; page 1**).

- FDA clarified that the utility of the data collected by Graceway for future trials would be the accumulation of placebo response data for patients with bacterial vaginosis. It is for general information purpose only, not for Graceway to conduct additional trials.
- FDA stated that for a new drug to be submitted for approval, two adequate well-controlled studies are typically needed. But in this case, of the safety and efficacy data available for the treatment of bacterial vaginosis with 0.75% metronidazole is supportive information, and only one Phase 3 study with 1.3% formulation would be needed. The adequacy of the 1.3% data that is collected will be assessed once it is submitted.
- FDA stated that the design of the Phase 3 study (described in the first page of the 2-page handout, **see attachment; page 1**) seemed acceptable on face value, but the detailed protocol will be reviewed when submitted. FDA noted contrary to what was presented on the handout, the primary analysis should be a Modified Intent to Treat (MITT), not Per Protocol, for a placebo controlled trial. The MITT population defined in the draft protocol (provided on page 32 of Attachment 4 in the briefing package) was acceptable by the Agency.
- FDA requested the collection of information to assess the placebo for irritation potential. Graceway responded that the clinical study will collect safety information including local application adverse events from all subjects including

placebo group. The placebo tolerability information would be compared to that of the 1.3% product. FDA found this to be acceptable.

- Graceway presented an overall estimate of patients that would be exposed to the 1.3% product from the three clinical studies that would be included in a marketing application (**see attachment; page 2**): 1) the completed Phase 2 study, 2) a pharmacokinetic study in healthy volunteers, and 3) a Phase 3 placebo controlled study. FDA found this accumulation of patient exposures would be sufficient for a marketing application.

Graceway requested that FDA clarify what the sources would be for previous findings of efficacy and what information would need to be included in a marketing application.

- FDA stated that there would be no need to re-submit information concerning the efficacy of the 0.75% product, and that a cross-reference to the information submitted within the approved NDA for MGV 0.75% would be sufficient to the extent that the old data is similar to that generated for the 1.3% product. Graceway would need to own the information, and Graceway confirmed that they are the owners of the Metrogel Vaginal Gel 0.75% NDA.
- FDA discussed whether it could be possible to analyze the previous 0.75% data using the current BV standards. Graceway stated that the patient inclusion criteria used for the 0.75% is not the same as those that would be used for the 1.3% product (using the current guidance).
- FDA stated that the legacy data from 0.75% MGV are sufficient to provide support for the 1.3% product, as FDA has already concluded that metronidazole is effective for treatment of BV. The information generated for the 1.3% product will be reviewed based on current standards. The 0.75% information is considered supportive, but it will not change the FDA's assessment of the 1.3% data at that time.
- The phase 2 study data will be considered as useful supportive information and will be considered in the review of the Phase 3 study data.

Minutes Preparer: Jacquelyn Smith, MA, Regulatory Project Manager, DSPTP

Concurrence: Eileen Navarro Almario, M.D., Acting Deputy Director, DSPTP

Phase III Study Design

- Randomized, Double Blind, Vehicle-controlled, Multicenter Study
 - 1.3% metronidazole vs. vehicle (placebo)
 - Single dose (~5 gm as evaluated in Phase II study)
- Endpoint: Therapeutic cure rate
 - Primary analysis: PP population
 - Supportive: MITT population
- Sample size: 146/group (PP), enroll approximately 450 (~10-12/site at ~40 sites)
 - Alpha of 0.05, 2-sided
 - $P_c=0.10$, $P_t=0.25$, Power=0.90, Dropout=~35%

Numbers (approximate) Exposed 1.3% Metronidazole

Study	Subjects Exposed (ITT/Safety)	Subjects Evaluable (PP)
Phase II (GW04-0904, all regimens)	189	140
PK Study (GW01-1005)	16	16
Phase III (GW05-1003)	225	146
Total	430	302

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/s/

EILEEN E NAVARRO ALMARIO
09/20/2010