

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205223Orig1s000

CHEMISTRY REVIEW(S)

NDA 205223

Metronidazole Vaginal Gel 1.3%

Valeant Pharmaceuticals North America LLC

Lin Qi, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division II, Branch V**

For the Division of Anti-Infective Products

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 205223
2. REVIEW #: 1
3. REVIEW DATE: Feb 4, 2014
4. REVIEWERS: Lin Qi
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA Submission
Amendment
Amendment

24-May-2013
14-Aug-2013
20-Nov-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Valeant Pharmaceuticals North America LLC
Address: 7720 North Dobson Road
Scottsdale, AZ 85256

Representative: Michael O'Beirne
Telephone: 480-291-5495
Email: mobeirne@medicis.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name: Metronidazole
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type:
 - Submission Priority: S

CMC Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Antimicrobial
11. DOSAGE FORM: Vaginal Gel
12. STRENGTH/POTENCY: 1.3%
13. ROUTE OF ADMINISTRATION: Topical
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
- SPOTS product – Form Completed
- Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	1/30/2014	
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107484	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	2/4/2014	R. Safaai-Jazi
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Adequate	2/4/2014	Lin Qi
DMEPA*	N/A		
EA	Categorical exclusion	2/4/2014	Lin Qi
Microbiology	Approval	6/21/2013	Brian S. Riley

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 205-223

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information as amended in the NDA is adequate to assure the identity, strength, purity, and quality of metronidazole vaginal gel 1.3%.

Draft labels and labeling have adequate CMC information. Final labels and labeling are pending team review as of the date of this review.

The site recommendation from the Office of Compliance is “Acceptable” dated Feb 4, 2014.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

None.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance, metronidazole, is a (b) (4), with a molecular formula of $C_6H_9N_3O_3$. Metronidazole is manufactured, controlled, and tested at (b) (4), while a DMF (b) (4) is referenced for detailed chemistry, manufacturing, and controls information. DMF (b) (4) was found adequate to support the current NDA in the latest review #13 dated Jan 30, 2014. Metronidazole is also tested for acceptance at DPT Laboratories, Ltd., Texas, according to the USP monograph. All tests, with the exception of Description, are per current USP (See Table S.4.1-1).

(2) Drug Product

The drug product, Metronidazole Vaginal Gel 1.3%, is an aqueous, slightly opaque, yellow gel supplied in 5 g pre-filled applicators. One full applicator of Metronidazole Vaginal Gel 1.3% contains 5 g of product to be applied intravaginally as a one-time dose. The product is formulated at a pH of approximately 4 to be compatible with the pH of the vaginal fluid. The gel formulation contains 1.3% w/w of metronidazole dissolved in a gel vehicle containing Polyethylene Glycol 400, Propylene Glycol, Benzyl Alcohol, Methylparaben, Propylparaben, Purified Water, and Polycarbophil. All excipients are compendial grade and within levels used in other approved vaginal drug products. Metronidazole vaginal gel 1.3% is manufactured, (b) (4), and tested at DPT Laboratories, Ltd, Texas via a (b) (4)

Executive Summary Section

(b) (4)

The drug product will be tested for Description, Identification (HPLC and TLC), pH, Minimum Fill (release only), Package Integrity, Viscosity, Assay for Metronidazole, Assay for Benzyl Alcohol, Assay for Methylparaben, Assay for Propylparaben, Impurities/Related Substances, and Microbial Tests. The pre-filled applicator barrel, plunger and cap are composed of HDPE ((b) (4)) and the piston is composed of (b) (4) rubber ((b) (4)). The applicator is manufactured by (b) (4). The applicator is overwrapped with flexible foil manufactured by (b) (4). There are no significant drug product changes in description, assays, impurities, package integrity, pH, weight loss, and viscosity observed on the 3 registration lots through 36 months under long-term storage at 25°C/60% RH and 6 months storage at 40°C/75% RH. The available stability data support the proposed expiry period of 36 months when stored under USP controlled room temperature conditions of 20°C to 25°C (68°F to 77°F) with allowed excursions between 15°C to 30°C.

B. Description of How the Drug Product is Intended to be Used

METRONIDAZOLE Vaginal Gel, 1.3% is indicated for the treatment of bacterial vaginosis in non-pregnant women. The drug product is supplied in a pre-filled applicator which delivers approximately 5 g of gel containing 65 mg of metronidazole. It is for intravaginal use only, not for ophthalmic, dermal, or oral use. Each single-dose, pre-filled disposable applicator is to be used once intravaginally at bedtime.

C. Basis for Approvability or Not-Approval Recommendation

This NDA has provided sufficient information on raw material controls, manufacturing processes and process controls, test methods, specifications, batch data and stability data for assuring consistent product quality of the drug substance and drug product over the storage period. The CMC information in the NDA, as amended, is sufficient to assure the identity, strength, purity, and quality of metronidazole vaginal gel, 1.3%.

The site recommendation from the Office of Compliance is “Acceptable” dated Feb 4, 2014.

Therefore, from the CMC perspective, this NDA is recommended for approval.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Lin Qi, Ph.D., CMC Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Dorota Matecka, Ph.D., CMC Lead, ONDQA

Rapti Madurawe, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DARRTS

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

/s/

LIN QI
02/04/2014

DOROTA M MATECKA
02/04/2014

RAPTI D MADURawe
02/05/2014

Initial Quality Assessment (IQA) and Filing Review

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **205223**

Submission Date: May 24, 2013
GRMP Goal Date: February 7, 2014
PDUFA Goal Date: March 24, 2014

2. PRODUCT PROPERTIES:

Trade or Proprietary Name:	<i>Not proposed in the original NDA submission*</i>
Established or Non-Proprietary Name (USAN) and strength:	Metronidazole vaginal gel, 1.3%
Dosage Form:	Vaginal gel

* It may be proposed later

3. APPLICANT:

Name:	Valeant Pharmaceuticals North America LLC
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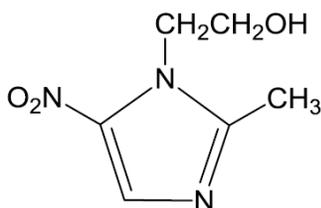
4. SUBMISSION PROPERTIES:

Review Priority :	Standard
Property (Legal Basis):	505 (b)(1)
Responsible Organization:	DAIP

Review Information

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Metronidazole [2-methyl-5-nitroimidazole-1-ethanol; 2-(5-nitro-2-methylimidazol-yl)ethanol]



$C_6H_9N_3O_3$
MW = 171.2

2. INDICATION: Topical treatment of bacterial vaginosis (BV) in non-pregnant women

3. ROUTE OF ADMINISTRATION: Vaginal

4. STRENGTH/POTENCY: 1.3%

5. Rx/OTC DISPENSED: Rx OTC

6. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Is this a SPOTS product? Yes No Not evaluated at time of IQA.

**Initial Quality Assessment (IQA) and Filing Review
NDA 205223**

7. RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	March 4, 2013	Last review dated August 5, 2011
(b) (4)	III	(b) (4)		February 20, 2013	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Clin Pharm	<input type="checkbox"/>	<input type="checkbox"/>	
EES	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Submitted and pending as of June 13, 2013
Pharm/Tox	<input checked="" type="checkbox"/>	<input type="checkbox"/>	TBD (if needed)
Methods Validation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	TBD (if needed)
EA	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Categorical exclusion claim
New Drug Micro	<input type="checkbox"/>	<input type="checkbox"/>	Done (approval recommended - review in DAARTS dated June 21, 2013)
CDRH	<input type="checkbox"/>	<input type="checkbox"/>	
Other ()	<input type="checkbox"/>	<input type="checkbox"/>	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND		107484	

d. Previous Communications with the Applicant to note (if any):

DOCUMENT NAME	Document DATE	APPLICATION NUMBER	DESCRIPTION
STP letter	01/20/2010	107484	CMC comments included
EoP2 meeting	08/23/2010	107484	Preliminary responses
EoP2 meeting	09/20/2010	107484	Meeting minutes
Pre-NDA meeting	02/15/2013	107484	Preliminary responses (meeting cancelled)

Initial Quality Assessment (IQA) and Filing Review
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Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	CMC Filing Issues
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the applicant with the 74 day letter?		
Yes	No	CMC Comments for 74 Day Letter
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<ol style="list-style-type: none">1. Please 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. <div style="background-color: #cccccc; height: 100px; width: 100%; margin-top: 5px;"></div>(b) (4)3. <div style="background-color: #cccccc; height: 100px; width: 100%; margin-top: 5px;"></div>(b) (4)4. Please provide 2 drug product samples in the commercial packaging configuration.

CMC Summary: Critical Issues and Complexities

CMC Critical Issues or Complexities			
<p>Metronidazole drug substance is an approved agent for the treatment of bacterial vaginosis (BV). The CMC information for the drug substance is provided in the current application via a reference to a Type II DMF ^{(b) (4)}. It should be noted that this DMF has been referenced for a number of approved products, including vaginal products containing metronidazole. The issues related to the drug product, a new formulation of metronidazole vaginal gel, have been described below, in the drug product section. Several issues have been identified as review issues and will be included in the 74-day letter (as listed above; comments 2-4 identified by the reviewer, Dr. Lin Qi).</p>			
Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is a team review recommended?			
Yes	No	Suggested expertise for team	
<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Review Team Assignments (if known)			
Drug Substance	Lin Qi		
Drug Product	Lin Qi		
Biopharmaceutics	Tapash Ghosh		
QbD	N/A		
Product Quality Microbiology	Brian S. Riley		
ONDQA PM	Navdeep Bhandari		

Summary or Highlights of the Application (not already mentioned in other sections)

**Initial Quality Assessment (IQA) and Filing Review
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Changes between Clinical DP and Proposed Commercial DP

Clinical	Commercial
No changes	

Metronidazole is a nitroimidazole classified as both an antibiotic and as an anti-protozoal agent.

Metronidazole drug substance has been approved as several dosage forms. The currently available metronidazole products for vaginal administration include MetroGel-Vaginal® (metronidazole vaginal gel), 0.75%, which has been approved since 1992 (NDA 20208) and has been used extensively for the treatment of BV, and Vandazole (metronidazole vaginal gel, 0.75%) approved in 2005 (NDA 21806). The current regimen of MetroGel-Vaginal, 0.75% calls for a five-day treatment. The proposed drug product, a new hydrogel formulation of metronidazole, Metronidazole Vaginal Gel 1.3%, with a higher concentration of metronidazole, has been developed with the intent to provide a single dose formulation that would be equally efficacious as the currently marketed products requiring five to seven days of treatment.

Metronidazole Vaginal Gel, 1.3% will be provided in a single dose applicator containing 5 g of the drug product (which contains 65 mg dose of metronidazole drug substance). Patients will be instructed to deliver the entire contents of the applicator once at bedtime.

Drug Substance

Some general information and information on the control of the metronidazole drug substance, including a specification, some information on impurities, and batch analysis data for the batches used in clinical studies has been provided in the NDA. The other CMC information such a description of the manufacturing process, controls of materials, process development and validation, stability, etc. is provided via a reference to DMF Type II (b) (4). *Comment: The drug substance specification (which seems to follow the USP monograph for metronidazole) has been attached to this review as Appendix 1.*

This DMF (originally submitted on September 3, 1979) has been referenced previously in other NDAs and ANDAs (e.g., NDAs 20208 and 21806). It was last reviewed on August 5, 2011 and found adequate. As indicated in DARRTS, a quality amendment was submitted on December 12, 2011. In addition, on October 23, 2012, this DMF was evaluated for completeness by the Office of Generic Drugs. *Comment: The amendment dated December 12, 2011 may need to be reviewed for the purpose of the current NDA review.*

Drug Product

The formulation of the proposed drug product, metronidazole vaginal gel, contains metronidazole, an anti-bacterial and anti-protozoal agent, at strength of 1.3% w/w in a gel vehicle containing polyethylene glycol 400, propylene glycol, benzyl alcohol,

Initial Quality Assessment (IQA) and Filing Review
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methylparaben, propylparaben, purified water, and polycarbophil. The drug product is a (b) (4). Metronidazole Vaginal Gel, 1.3% will be supplied in pre-filled, single use intravaginal applicators. Each applicator contains 5 g of product to be administered as a one-time dose.

The qualitative and quantitative composition of the proposed drug product (metronidazole vaginal gel) been attached as Appendix 2 (below). Per applicant, all excipients used in the proposed gel formulation, are compendial. The product has been formulated at a pH of approximately 4 to be compatible with the pH of the vaginal fluid. The applicant stated that the formulation used in all pharm/tox and clinical studies is the same as the proposed commercial formulation.

In brief, the proposed manufacturing process consists of (b) (4)

at DPT Laboratories, San Antonio, TX, where all drug product lots used in clinical, toxicology, and registration lots used in the primary stability studies were manufactured. The commercial drug product lots will be manufactured at the DPT San Antonio site.

The primary container closure system that was used for drug product in clinical studies will also be used for the proposed commercial product. The container closure system consists of 5 g pre-filled applicators. The applicator barrel, plunger and cap are composed of HDPE ((b) (4)) and the piston is composed of (b) (4) rubber ((b) (4) DMF # (b) (4)).

The applicator is manufactured by (b) (4). The secondary packaging consists of flexible aluminum foil overwrap. Information on suitability of the proposed container including extraction studies has been provided in section 3.2.P.7. *Comment: This information should be evaluated carefully during the NDA review for applicability to the proposed product. For example, the applicant used (b) (4)*

This may need to be reevaluated. Also, the toxicological evaluation of the identified extractables may need to be consulted with the pharm/tox reviewer. In addition, data demonstrating that the proposed applicator delivers a consistent dose of 5 gram should also be submitted (see comments for the 74-day letter).

The proposed drug product specification includes the following tests: description, identification (by HPLC and TLC), pH minimum fill, package integrity, Viscosity, assay (metronidazole, benzyl alcohol, methylparaben, and propylparaben), impurities/related substances, and microbial limits. In addition, antimicrobial effectiveness was evaluated for the proposed formulation. *Comment: It should be noted that this application has been evaluated by the product quality microbiology reviewer (Dr. Brian Riley) who recommended this application for approval from the standpoint of product quality microbiology (refer to the review dated June 21, 2013 in DARRTS). The overall acceptability of the drug product specification should be further evaluated during*

**Initial Quality Assessment (IQA) and Filing Review
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the NDA review based on the batch analysis data and stability data (e.g., since the weight loss evaluation conducted on stability did not show any significant change, the applicant has proposed to remove it from the drug product specification). It should also be noted that Dr. Tapash Ghosh has evaluated the application and concluded that there are no issues from the biopharmaceutics perspective; therefore, no biopharmaceutics review is needed.

Stability data have been conducted for three registration production scale batches manufactured by DPT (and as stated by the applicant, packaged in to be marketed final packaging configuration) according to the table below:

Table 1. Stability Data for Primary Registration and Clinical Lots

Lot Number	Batch Size	Packaging Size	Test Condition	Long-Term Data Provided in this Submission
EBX-C ^a	(b) (4)	5 gram	25°C/60% RH	9 months
BGC-C ^b		5 gram	25°C/60% RH	36 months
			40°C/75% RH	6 months
			Freeze/Thaw	
BLN-C ^{a,b}		5 gram	25°C/60% RH	36 months
			40°C/75% RH	6 months
			Freeze/Thaw	
BMC-C ^b		5 gram	25°C/60% RH	36 months
			40°C/75% RH	6 months
			Freeze/Thaw	

^a Clinical Lot

^b Primary Registration Lot

In addition, freeze/thaw studies (3 cycles of -20 deg C/45 deg C) were also conducted for the three registration batches. *Comment: As indicated by the chemistry reviewer, Dr. Lin Qi, only data for the first cycle were submitted. The applicant should submit data for the third cycle as well (see comments for the 74-day letter).*

The expiry period of 36 months has been proposed by the applicant for the proposed drug product when stored under USP controlled room temperature of 20 deg C to 25 deg C (68 deg F to 77 deg F) with allowed excursions between 15 deg C to 30 deg C.

Description of Facility-Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

The proposed commercial drug substance facility is (b) (4) located in (b) (4). Drug product manufacturing facility is DPT Laboratories in San Antonio, Texas. See EES for complete list of facilities related to this application.

Initial Quality Assessment (IQA) and Filing Review
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FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	CMC information submitted per CTD (Modules 2 and 3).
3.	Are all the pages in the CMC section legible?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Attachment to FDA Form 356h dated May 24, 2013.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	<input type="checkbox"/>	<input type="checkbox"/>	N/A

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7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As above
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As above
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As above

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10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

D. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
13.	Does the section contain a description of the DS manufacturing process?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4) (LoA dated March 4, 2013 has been provided)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS in process parameters?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4).
15.	Does the section contain information on impurities?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	yes
16.	Does the section contain information regarding the characterization of the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4).
17.	Does the section contain controls for the DS?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4).
18.	Has stability data and analysis been provided for the drug substance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4).
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
21.	Does the section contain container and closure information?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Reference to DMF Type II (b) (4).

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F. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
22.	Does the section contain quality controls of excipients?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
23.	Does the section contain information on composition?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
26.	Is there a batch production record and a proposed master batch record?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Provided in section 3.2.R. Regional Information (executed manufacturing and packaging records for Lot BGC-C; also, a proposed master manufacturing batch record has been included)
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	The formulation used in all tox and clinical studies is the proposed commercial formulation.
28.	Have any Comparability Protocols been requested	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Pre-filled plastic (HDPE) applicators (5 gram) with aluminum overwrap
30.	Does the section contain controls of the final drug product?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
31.	Has stability data and analysis been provided to support the requested expiration date?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Stability data submitted in section 3.2.P.8.3 include data for 3 registration batches (as described above)
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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G. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
34.	Is there a methods validation package?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

H. MICROBIOLOGY				
	Parameter	Yes	No	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A (not a sterile product)

I. LABELING				
	Parameter	Yes	No	Comment
36.	Has the draft package insert been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
37.	Have the immediate container and carton labels been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Draft overwrap and carton labels submitted
38.	Does section contain trade name and established name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Established name only (metronidazole vaginal gel).

FILING CONCLUSION				
	Parameter	Yes	No	Comment
39.	ARE THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>		
40.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
41.	Are there any potential review issues identified?	<input checked="" type="checkbox"/>		<i>See comments above (page 4 of this review).</i>

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REVIEW AND APPROVAL

See appended electronic signature page

Dorota Matecka, Ph.D.

CMC Lead

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

See appended electronic signature page

Rapti Madurawe, Ph.D.

Branch Chief

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

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Appendix 1. DS Specification

Table 1. Drug Product Manufacturer's Specification for Incoming Drug Substance

Test	Method	Specification
Description	73.4009	(b) (4)
Identification:		
FTIR	USP<197A>	Conform
HPLC	USP	Conform
Loss on drying	USP <731>	NMT (b) (4) %
Residue on ignition	USP <281>	NMT (b) (4) %
Heavy metals	USP Met II<231>	NMT (b) (4) %
(b) (4) (b) (4) (HPLC)	USP <621>	NMT (b) (4) %
Single unspecified impurity (HPLC)	USP <621>	NMT (b) (4) %
Total impurities (HPLC)	USP <621>	NMT (b) (4) %
Assay	USP	(b) (4) %
(b) (4)	USP <467>	Meets requirements per option 1 limits
(b) (4)	USP <467>	NMT (b) (4) PPM (b) (4) %

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Appendix 2. DP Composition

Table 1. Drug Product Components and Composition

Component	Function	Quality Standard	Quantity (% w/w)	Quantity (g per 5 g)
Polyethylene Glycol 400	(b) (4)	NF	(b) (4)	(b) (4)
Propylene Glycol		USP		
Benzyl Alcohol		NF		
Methylparaben		NF		
Propylparaben		NF		
Metronidazole		USP		
Purified Water		USP		
Polycarbophil		USP		

NF = National Formulary

USP = United States Pharmacopeia

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Appendix 3. DP Specification

Table 1. Drug Product Specification

Test	Method	Limit
Description	Visual [73.4009] [73.7286]	(b) (4)
Identification (HPLC)*	HPLC (In-house) [73.6663]	Retention time of the principal peak in the assay sample is in concordance with the principal peak in the reference standard.
Identification (TLC)*	USP <201>	Pass
pH	USP <791>	(b) (4)
Minimum fill*	USP <755>	NLT (b) (4) % of labeled quantity
Package Integrity	[73.4352]	Pass
Viscosity	USP <912>	(b) (4) cP
Assay:		
Metronidazole	HPLC (In-house) [73.6663]	(b) (4) % labeled claim (b) (4) % w/w
Benzyl alcohol		(b) (4) % labeled concentration (b) (4) % w/w
Methylparaben		(b) (4) % labeled concentration (b) (4) % w/w
Propylparaben		(b) (4) % labeled concentration (b) (4) % w/w
Impurities/Related Substances		
(b) (4)	HPLC (In-house) [73.6761]	NMT (b) (4) %
		NMT (b) (4) %
		NMT (b) (4) %
Microbial enumeration:		
Total aerobic microbial count	USP <61>	NMT (b) (4) cfu/g
Total yeasts and molds count		NMT (b) (4) fu/g
Specified microorganisms:		
<i>Staphylococcus aureus</i>	USP <62>	(b) (4)
<i>Pseudomonas aeruginosa</i>		
<i>Candida albicans</i>	USP <62>	

* Performed at release only

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

/s/

DOROTA M MATECKA
07/24/2013

RAPTI D MADURawe
07/24/2013