CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 202121

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	202121		
Drug Product Name	Progesterone Capsule		
Strength (s)	100 mg and 200 mg		
Applicant Name	Teva Pharmaceuticals, USA		
Address	400 Chestnut Ridge Road Woodcliff Lake, NJ 07677		
Applicant's Point of Contact	Robert S. Vincent, Director – Regulatory Affairs		
Contact's Phone Number	(201) 930-3610 or (210) 930-2233		
Contact's Fax Number	(201) 489-1403		
Submission Date(s)	June 11, 2010		
First Generic	NO		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	11036003	3716	
Study Type (s)	Fasting	Fed	
Strength(s)	200 mg	200 mg	
Clinical Site	Novum Pharmaceutical Research Services	Biovail Contract Research (a Division of Biovail Corporation)	
Clinical Site Address	3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739	460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6 Tel: (416) 752-3636 / (416) 686-6334 Fax: (416) 752-7610 / (416) 690-1880	
Analytical Site	(b) (4)		
Analytical Address			
OUTCOME DECISION	**INADEQUATE**		
BE STUDY TRACKING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
# 1	**Dissolution**	100 mg and 200 mg	**INADEQUATE**

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only for ANDA # 202121, Progesterone Capsules, 100 mg and 200 mg. The DBE will review the fasted and fed BE studies, as well as the bio-waiver request at a later date. The application references NDA # 019781, PROMETRIUM®, 100 mg and 200 mg, manufactured by Abbott Prods (approved on May 14, 1998 and October 15, 1999 for the 100 mg and 200 mg strengths, respectively). PROMETRIUM® Capsules are indicated for use in the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.

There is no USP method for this product. The DBE external database recommends the firm develop a quantitative rupture test[1]. Currently, there is no recommendation on the DBE internal database.

The NDA dissolution method is considered unconventional and thus the method is not recommended for generic versions of PROMETRIUM® Capsules[2]. The firm submitted its own comparative dissolution method which is not appropriate for the IR product. The firm submitted the results of comparative dissolution testing using the following dissolution method and did not propose any specification:

Apparatus:	USP apparatus I (Basket, 20 mesh)
Speed:	100 rpm
Medium:	5% SDS in 0.1 N HCl
Volume:	1000 mL
Sampling:	2 hrs, 4 hrs, 6 hrs, 8 hrs, and 10 hrs

The reviewer notes that the submitted data are discriminatory and reach complete dissolution for both strengths in 6 hours for this IR product. The DBE will request an additional dissolution using a different method. Therefore, the dissolution testing data is **incomplete (inadequate)** at this time. The firm will be informed of the DBE's decision in a deficiency letter.

[1] http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm
[2] V:\FIRMSNZ \ (b) (4) CONTROLS \02486c0802.doc

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	☐	☒
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☒	☐	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☒
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are the DBE Summary Tables present and in either PDF and/or MS Word Format?			☒	☐	☐
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?			☒	☐	☐
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Baskets, 20 Mesh)
	Speed of Rotation:	100 rpm
	Medium:	5% SDS in 0.1 HCl
	Volume:	1000 mL
	Temperature:	37.0 ± 0.5˚C
Firm's Proposed Specifications	Meets current USP <905> acceptance value and range (as specified) L=1 15.0 and 25.0	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. (Subsidiary of Teva Pharmaceuticals USA) 223 Quaker Road Pomona, NY 10970	

Study Ref No.	**Testing Dates**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**	
Study Report #: ARD-RPT-4538	03/01/2010 03/02/2010	Test Product Name: Progesterone Capsules, 100 mg Batch No.: 0001019501 Manufacturing Date: 01/05/2010	100 mg Capsules	12	Mean	43	83	96	97	97	Module 5.3.1.3
					Range	(b) (4)					
					%CV	5.5	8.1	2.6	1.4	1.5	
Study Report #: ARD-RPT-4538	03/01/2010 03/02/2010	Reference Product Name: PROMETRIUM® (progesterone, USP) Capsules, 100 mg Lot No.: 500309 Expiration Date: September 2011	100 mg Capsules	12	Mean	46	81	92	95	96	
					Range	(b) (4)					
					%CV	8.4	12.6	9.8	5.3	3.0	

Progesterone Capsules, 100 mg Batch Number 0001019501 Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)					
Capsule #	**% Dissolved**				
	2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	**43**	**83**	**96**	**97**	**97**
Max	(b) (4)				
Min					
% RSD	**5.5**	**8.1**	**2.6**	**1.4**	**1.5**
Reference	PR8868/88-89				
Date of testing	03/01/2010, 03/02/2010				

Prometrium® (progesterone, USP) Capsules 100 mg LOT: 500309 EXP: SEPT 2011 Manufactured by Solvay Pharmaceuticals					
Capsule #	**% Dissolved**				
	2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	**46**	**81**	**92**	**95**	**96**
Max	(b) (4)				
Min					
% RSD	**8.4**	**12.6**	**9.8**	**5.3**	**3.0**
Reference	PR8868/88-89				
Date of testing	03/01/2010, 03/02/2010				

Comparative Dissolution Profiles Study

Progesterone Capsules, 100 mg

Batch Number: 0001019501

Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)

VS

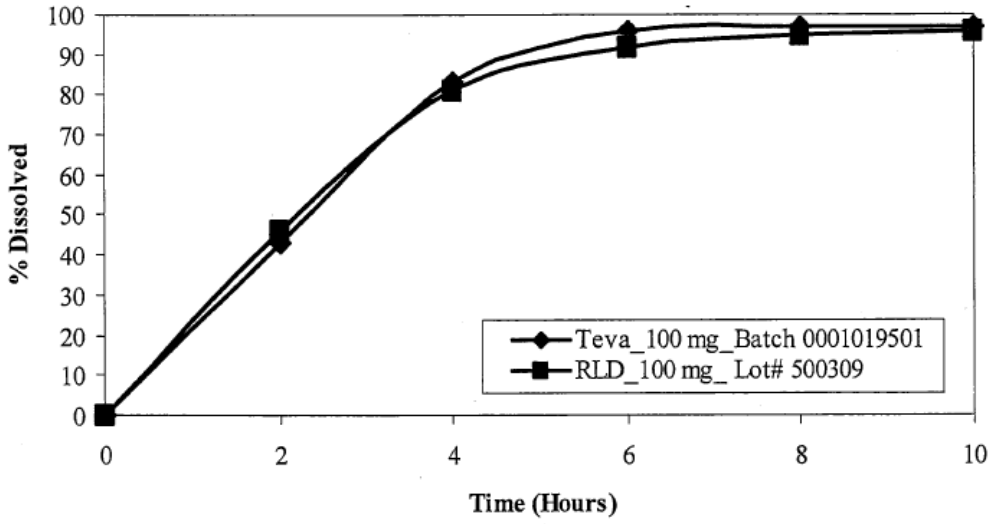
Prometrium® (progesterone, USP) Capsules 100 mg

LOT: 500309 EXP: AUGUST 2012

Manufactured by SOLVAY PHARMACEUTICALS

(Average of 12 Capsules)

Figure 1



Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Baskets, 20 Mesh)
	Speed of Rotation:	100 rpm
	Medium:	5% SDS in 0.1 HCl
	Volume:	1000 mL
	Temperature:	37.0 ± 0.5˚C
Firm's Proposed Specifications	Meets current USP <905> acceptance value and range (as specified) L=1 15.0 and 25.0	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. (Subsidiary of Teva Pharmaceuticals USA) 223 Quaker Road Pomona, NY 10970	

Study Ref No.	**Testing Dates**	**Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**					**Study Report Location**
						2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**	
Study Report #: ARD-RPT-4528	02/03/2010 02/04/2010	Test Product Name: Progesterone Capsules, 200 mg Batch No.: 0001019502 Manufacturing Date: 01/05/2010	200 mg Capsules	12	Mean	28	58	83	93	95	Module 5.3.1.3
					Range	(b) (4)					
					%CV	9.8	11.8	11.4	4.7	2.1	
Study Report #: ARD-RPT-4528	02/03/2010 02/04/2010	Reference Product Name: PROMETRIUM® (progesterone, USP) Capsules, 200 mg Lot No.: 500509 Expiration Date: August 2012	200 mg Capsules	12	Mean	28	71	94	96	97	
					Range	(b) (4)					
					%CV	7.1	15.5	9.2	4.4	1.2	

Progesterone Capsules, 200 mg Batch Number 0001019502 Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)					
Capsule #	**% Dissolved**				
	2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**
1	[redacted] (b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	**28**	**58**	**83**	**93**	**95**
Max	[redacted] (b) (4)				
Min					
% RSD	**9.8**	**11.8**	**11.4**	**4.7**	**2.1**
Reference	PR9017/28-29				
Date of testing	02/03/2010, 02/04/2010				

Prometrium® (progesterone, USP) Capsules 200 mg LOT: 500509 EXP: AUG 2012 Manufactured by Solvay Pharmaceuticals					
Capsule #	**% Dissolved**				
	2 hours	**4 hours**	**6 hours**	**8 hours**	**10 hours**
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	**28**	**71**	**94**	**96**	**97**
Max	(b) (4)				
Min					
% RSD	**7.1**	**15.5**	**9.2**	**4.4**	**1.2**
Reference	PR9017/28-29				
Date of testing	02/03/2010, 02/04/2010				

Comparative Dissolution Profiles Study

Progesterone Capsules, 200 mg

Batch Number: 0001019502

Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)

VS

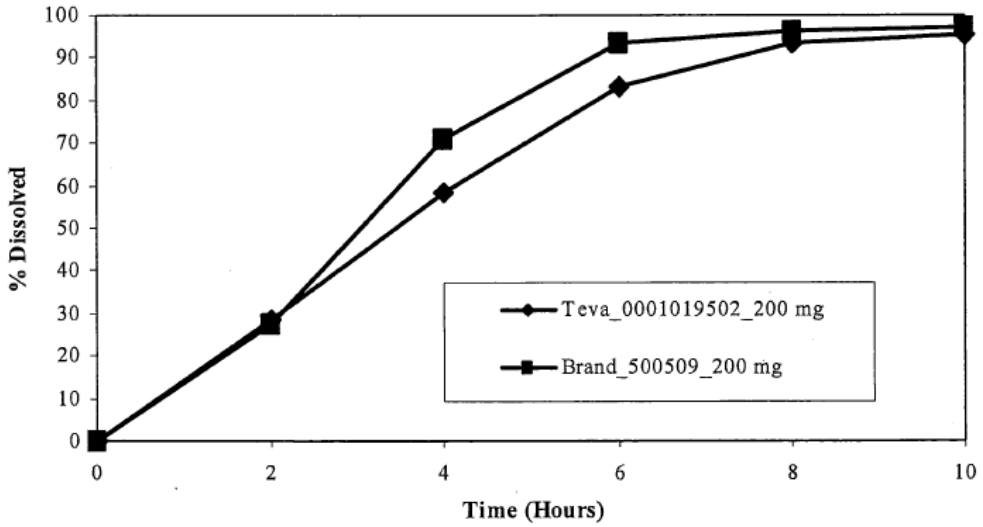
Prometrium® (progesterone, USP) Capsules 200 mg

LOT: 500509 EXP: AUGUST 2012

Manufactured by SOLVAY PHARMACEUTICALS

(Average of 12 Capsules)

Figure 1



II. COMMENTS:

1. There is no USP method for Progesterone Capsules. Also there is no specific DBE-recommended dissolution test method currently (November 26, 2010) available in the public or internal dissolution database on the Office of Generic Drugs website (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm).

2. The dissolution method and specification of the RLD PROMETRIUM® Capsules is as follows1[3]:

Apparatus: BIODIS II at 20 DPM*
Medium: 250 mL of 30/70 1-Propanol/0.1 N HCl
Temperature: 37 C ± 0.5C
Detection: UV at 244 nm
Specification: NLT (b) (4)(Q) in 45 minutes[4]

3. Per Control 02-486, "*The NDA dissolution method is considered unconventional and this method is not recommended for generic versions of Prometrium Capsules*". Instead the firm is recommended to develop their own method.

4. In the current application, the firm conducted dissolution testing using their own proposed method. The firm submitted dissolution testing data using the following dissolution method[5]:

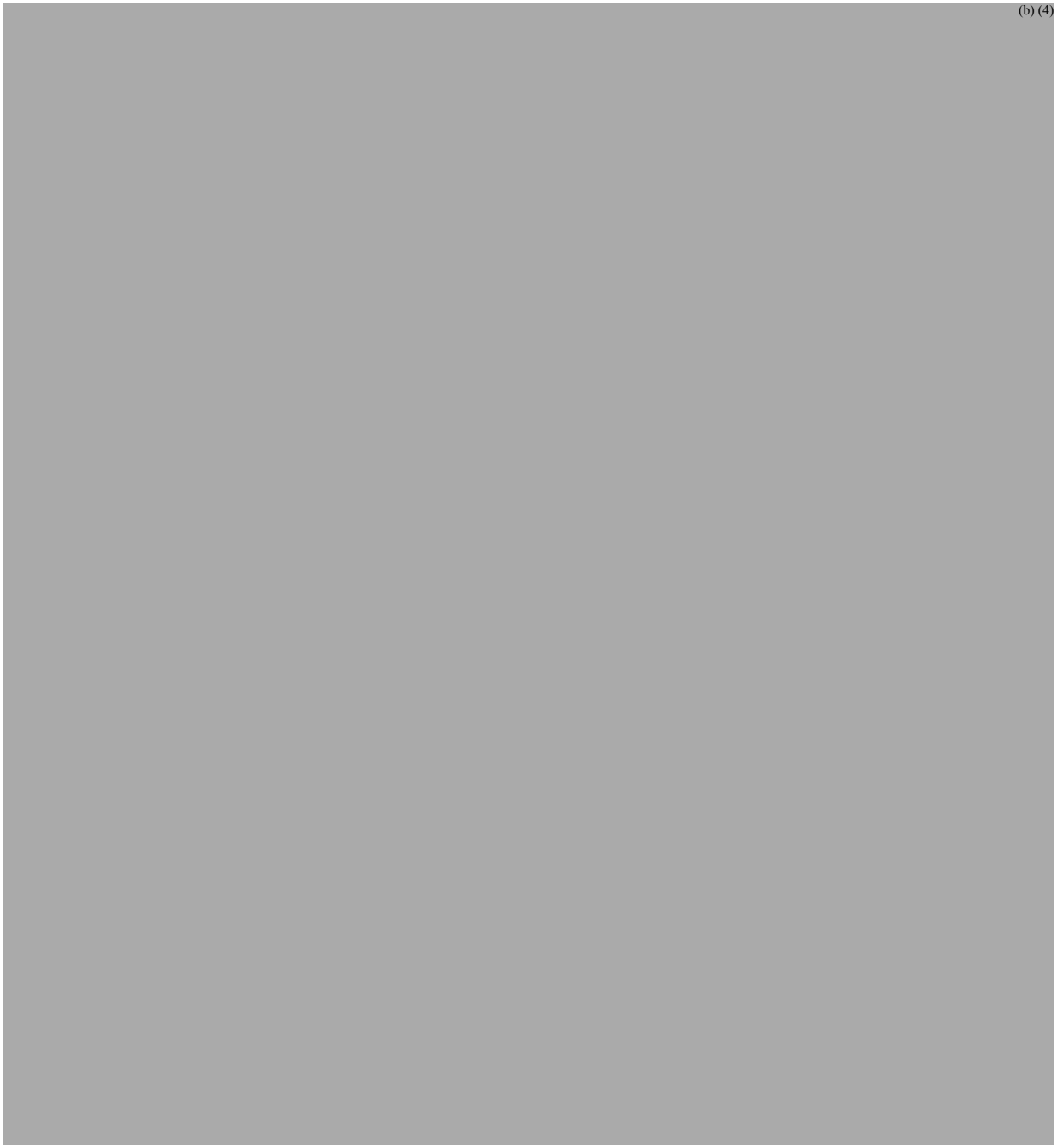
Apparatus:	USP apparatus I (Basket, 20 mesh)
Speed:	100 rpm
Medium:	5% SDS in 0.1 N HCl
Volume:	1000 mL
Sampling:	2 hrs, 4 hrs, 6 hrs, 8 hrs, and 10 hrs

The reviewer feels that the above mentioned sampling points are not appropriate for the IR product therefore he will recommend additional dissolution data.

5. The reviewer checked the dissolution data for (b) (4) other in-house ANDA applications for Progesterone Capsules (ANDA (b) (4). The proposed dissolution methods and specifications for these applications were as follows:

(b) (4)

[3] V:\FIRMSNZ \(b) (4)\ CONTROLS \02486c0802.doc
[4] DARRTS: TANG, ZHE J 10/23/2009 N/A 10/23/2009 REV-QUALITY-03(General Review)
[5] The individual capsule data can be found in module 5.3.1.3 of the application.



6. The dissolution method and specification will not be set until such time that the firm has submitted all of the requested comparative dissolution testing data.

7. The storage period of bio-study samples was 27 days at -22°C for the fasting study and 87 days at -22°C for the fed study. The long-term storage stability (LTSS) data for progesterone was demonstrated for 176 days at -22°C and 124 days at -22°C for the fasting and fed studies, respectively. Therefore, the LTSS data exceed the storage

duration of the bio-study samples for both the fasted and fed BE studies. These results are adequate.

8. The firm submitted the appropriate SAS Transport files (.xpt), as well as the DBE Summary Tables # 1-16 in electronic format.

III. DEFICIENCY COMMENTS:

The firm's dissolution method is not appropriate for this IR product for being too slow. The DBE will make the similar recommendation to this firm as it did to (b) (4) for its ANDA (b) (4).

IV. RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Teva Pharmaceuticals, USA on its test product, Progesterone Capsules, 100 mg and 200 mg, comparing both strengths to Abbott Prods PROMETRIUM® Capsules, 100 mg and 200 mg, is incomplete (inadequate) due to the reasons stated in above Deficiency Comments section.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 202121

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Progesterone Capsule, 100 mg and 200 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the fasted and fed *in vivo* bioequivalence studies and bio-waiver request will be conducted later. The following deficiencies have been identified:

1. The dissolution data using your own proposed method demonstrated slow dissolution profiles for both test and reference products. It takes 6 to 8 hours to achieve complete dissolution of this Immediate Release (IR) product. The DBE recommends that you conduct additional dissolution testing with further modification of your proposed method such as increasing concentration of surfactant to shorten dissolution testing time if possible. Alternatively, the DBE recommends that you consider developing a dissolution method using USP Apparatus II (Reciprocating Cylinder) or USP Apparatus IV (Flow Cell). For helpful considerations in dissolution method development for the current dosage form, please refer to the article on "Liquid-filled Gelatin Capsules" in the "Stimuli to Revision Process" section of volume 35(4) of USP-PF (http://www.usppf.com/pf/pub/index.html). The DBE suggests the following method as an example.

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Sampling times	15, 30, 45 and 60 minutes or till 80% is dissolved.

*To avoid excess foam formation, two drops of simethicone should be added.

2. For the further evaluation of your proposed dissolution method for the test product as requested in Comment 1 above, please submit your dissolution method development report.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 202121

Reviewer: DeHaven, Wayne **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Progesterone Capsules, 100 mg and 200 mg

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
12671	6/11/2010	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

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

/s/

WAYNE I DEHAVEN
12/01/2010

SHRINIWAS G NERURKAR
12/01/2010

HOAINHON N CARAMENICO on behalf of DALE P CONNER
12/01/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202121		
Drug Product Name	Progesterone Capsule		
Strength(s)	100 mg and 200 mg		
Applicant Name	Teva Pharmaceuticals, USA		
Address	400 Chestnut Ridge Road Woodcliff Lake, NJ 07677		
Applicant's Point of Contact	Robert S. Vincent, Director – Regulatory Affairs		
Contact's Telephone Number	(201) 930-3610 or (210) 930-2233		
Contact's Fax Number	(201) 489-1403		
Original Submission Date(s)	June 11, 2010		
Submission Date(s) of Amendment(s) Under Review	March 3, 2011 (new dissolution data submitted)		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	11036003	3716	
Study Type (s)	Fasting	Fed	
Strength (s)	200 mg	200 mg	
Clinical Site	Novum Pharmaceutical Research Services	Biovail Contract Research (a Division of Biovail Corporation)	
Clinical Site Address	3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739	460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6 Tel: (416) 752-3636 / (416) 686-6334 Fax: (416) 752-7610 / (416) 690-1880	
Analytical Site	(b) (4)		
Analytical Address			
OUTCOME DECISION	**INADEQUATE**		
Waiver Request Result	**INADEQUATE**		
DSI Report Result	**INADEQUATE**		
BE Study Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
	Dissolution	(b) (4) 100 mg, 200 mg and (b) (4)	**ADEQUATE**
	Fasting Study	(b) (4)	**INADEQUATE**
	Fed Study		**INADEQUATE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Teva's Progesterone Capsule, 200 mg, to the corresponding reference listed drug (RLD) Abbott's Prometrium® (Progesterone) Capsule, 200 mg. Each of the BE studies was designed as a single-dose, two-treatment, three-way, partial replicate crossover study in healthy post-menopausal female subjects. The fed study was carried out on 2 groups. The reference-scaled average BE approach was used to calculate the BE statistics for both studies. The firm measured baseline progesterone levels at -1, -0.5 and 0 hours prior to dosing, per the currently posted draft guidance on this product[1]. The means of the pre-dose progesterone levels were used for the baseline adjustment of the post-dose progesterone plasma levels. The firm submitted and analyzed the data using both adjusted and unadjusted data.

The results of the fasting and fed BE studies meet bioequivalence criteria for both baseline adjusted and unadjusted datasets; however, the BE studies are considered **incomplete (inadequate)** at this time (please see section 3.10 Deficiency Comments for details). The BE study results are summarized in the following tables (for simplicity only the baseline adjusted results are shown):

Progesterone Capsule
200 mg (1 x 200 mg)
Fasting BE Study No. 11036003, n = 39 (all post-menopausal females)
Summary of Statistical Analysis – Unscaled Data
Least Square Geometric Means, Point Estimates and 90% Confidence Intervals

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
AUC0-t (hr *pg/ml)	13956.97	13882.05	1.01	89.96	112.36
AUC∞ (hr *pg/ml)	18080.84	17752.97	1.02	88.93	116.64
Cmax (pg/ml)	3568.13	3672.89	0.97	84.45	111.75

Scaled Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (hr *pg/ml)	1.01	89.96	112.36	0.1453518	0.3812504	-0.08159	Scaled/PE	**PASS**
AUC∞ (hr *pg/ml)	1.05	88.93	116.64	0.1680042	0.4098831	-0.072659	Scaled/PE	**PASS**
Cmax (pg/ml)	0.97	84.45	111.75	0.1750762	0.418421	-0.092164	Scaled/PE	**PASS**

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf

Progesterone Capsule 200 mg (1 x 200 mg) Fed BE Study No. 3716, n = 100 (all post-menopausal females) Summary of Statistical Analysis – Unscaled Data Least Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	42.56	44.66	0.95	86.49	104.97
LCMAX	18.01	18.54	0.97	83.47	113.12

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (ng·hr/mL)	0.95	86.49	104.97	0.4338851	0.6586996	-0.274693	Scaled/PE	PASS
AUC∞ (ng·hr/mL)	0.90	.	.	0.4488096	0.6699325	-0.246303	Scaled/PE	PASS
Cmax (ng/mL)	0.97	83.47	113.12	1.0730172	1.0358654	-0.688154	Scaled/PE	PASS

There is a "dissolution only" review which can be found in DARRTS [see in DARRTS for ANDA #202121 DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive]. The dissolution testing was deemed unacceptable because the proposed method demonstrated slow dissolution profiles for both the test and reference products (6-8 hours to achieve complete dissolution of this immediate release product). The firm was asked to develop a new dissolution method which is more representative of the immediate release (IR) formulation. As a suggestion, the DBE recommended the following dissolution method used in ANDA (b) (4) [see in DARRTS for ANDA (b) (4) LU, FANG 06/11/2010 N/A 06/11/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive].

Media: 4.0 % of SLS Phosphate Buffer pH 6.8*
Volume: 250 mL
Temperature: 37 °C ± 0.5 °C
USP Apparatus: III (Reciprocating Cylinder)
Top Screen: 30 mesh
Bottom Screen: 40 mesh
Sinker: yes
Speed: 30 dip/minute
Sampling times: 15, 30, 45 and 60 minutes or till 80% is dissolved.

*To avoid excess foam formation, two drops of simethicone should be added.

In an amendment dated 03/03/2011, Teva responded to the "dissolution only" review deficiency letter by submitting new comparative dissolution data using the aforementioned method. These new data are acceptable. The firm will be informed that the DBE acknowledges its proposed specification of NLT (b) (4)(Q) dissolved in 45 minutes.

The formulation for the 100 mg strength of the test product is proportionally similar to that of the 200 mg strength of the test product which underwent bioequivalence testing. The dissolution testing for the 100 mg strength of the test product is acceptable. However, a waiver of the *in vivo* bioequivalence study requirement for the 100 mg strength cannot be granted at this time due to incomplete *in vivo* BE studies on the 200 mg capsules.

The clinical site for the fasting study (Novum Pharmaceuticals) is pending the outcome of routine inspection for ANDA (b) (4)[for details, see Section 7 'Attachments' in the following review located in DARRTS for ANDA (b) (4) WAHBA, ZAKARIA Z 06/17/2011 N/A 06/17/2011 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive]. The clinical site for the fed study (Biovail) was last inspected on (b) (4) for NDA (b) (4) and the outcome was VAI. The analytical site (b) (4) (b) (4) was last inspected on (b) (4) for ANDA (b) (4) and the outcome was VAI. The impact of the VAI findings will be reviewed at such time when the routine inspection for the clinical site (Novum) is completed.

The application is **incomplete (inadequate)** at this time.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Progesterone Capsules, 100 mg and 200 mg
Reference Product	PROMETRIUM® (Progesterone, USP) Capsules, 100 mg and 200 mg
RLD Manufacturer	Abbott Prods
NDA No.	019781
RLD Approval Date	100 mg: May 14, 1998 200 mg: October 15, 1999
Indication	PROMETRIUM® Capsules are indicated for use in the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea[3].
TE Code	None Listed in OB

3.2 PK/PD Information[2,4]

Bioavailability

After oral administration of progesterone as a micronized soft-gelatin capsule formulation, maximum serum concentrations were attained within 3 hours. The absolute bioavailability of micronized progesterone is not known. The Table below summarizes the mean pharmacokinetic parameters in postmenopausal women after five oral daily doses of PROMETRIUM® Capsules 100 mg as a micronized soft-gelatin capsule formulation.

PROMETRIUM Capsules Daily Dose			
Parameter	**100 mg**	**200 mg**	**300 mg**
Cmax (ng/mL)	17.3 ± 21.9[a]	38.1 ± 37.8	60.6 ± 72.5
Tmax (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC0-10 (ng*hr/mL)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

[a] Mean ± S.D.

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of PROMETRIUM Capsules 100 mg over the dose range 100 mg/day to 300 mg/day in postmenopausal women. Although doses greater than 300 mg/day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 mg/day and 400 mg/day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

Distribution: Progesterone is approximately 96% to 99% bound to serum proteins, primarily to serum albumin (50% to 54%) and transcortin (43% to 48%).

Food Effect

Concomitant food ingestion increased the bioavailability of

[2] http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=019781&TABLE1=OB_Rx
[3] http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=PROMETRIUM
[4] http://www.clinicalpharmacology-ip.com/Forms/search.aspx?s=prometrium

	PROMETRIUM® Capsules relative to a fasting state when administered to postmenopausal women at a dose of 200 mg.
Tmax	Approximately 1.5 – 2.5 hours
Metabolism	Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the gut via reduction, dehydroxylation, and epimerization.
Excretion	The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.
Half-life	The plasma elimination half-life ranges 5—20 minutes.
Drug Specific Issues (if any)	**WARNINGS** Progestins and estrogens should not be used for the prevention of cardiovascular disease. The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. The Women's Health Initiative Memory Study (WHIMS), a sub-study of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. Other doses of oral conjugated estrogens with medroxyprogesterone and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials. In the absence of comparable data and product-specific studies, the relevance of the WHI findings to other products has not been established. Therefore, the risks should be assumed to be similar for all estrogen and progestin products. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

3.3 OGD Recommendations for Drug Product[5]

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Partial or fully replicated crossover design in-vivo
	Strength:	200 mg
	Subjects:	Healthy males and postmenopausal females, general population. As many postmenopausal women as possible should be included in the study.
	Additional Comments:	Please measure baseline progesterone levels at -1.0, -0.5, and 0 hours before dosing. The mean of the pre-dose progesterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. Please analyze the data using both uncorrected and corrected data. Applicants may consider using a reference-scaled average bioequivalence approach for progesterone. If using this approach, please provide evidence of high variability in the bioequivalence parameters of AUC and/or Cmax (i.e., within-subject variability $\geq$ 30%). For detailed information on this approach, please refer to the published book chapter, Davit B, Conner D. Reference-scaled average bioequivalence approach. In: Kanfer I, Shargel L, eds. Generic Drug Product Development – International Regulatory Requirements for Bioequivalence. New York, NY: Informa Healthcare, 2010: 271-272.

2.	**Type of study:**	Fed
	Design:	Partial or fully replicated crossover design in-vivo
	Strength:	200 mg
	Subjects:	Healthy males and postmenopausal females, general population. As many postmenopausal women as possible should be included in the study.
	Additional Comments:	Please see additional comments above.

Analytes to measure (in plasma/serum/blood):	Progesterone in plasma
Bioequivalence based on:	90% CI for Progesterone
Waiver request of in-vivo testing:	100 mg
Source of most recent	Draft Guidance on Progesterone[6]

[5] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf

[6] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf

recommendations:	
Summary of OGD or DBE History:	There is no approved ANDA for the generic version of Prometrium® Capsule, 100 mg and 200 mg, listed on Orange Book (accessed on 06/2011). The OGD has received the following ANDAs regarding this drug product: [redacted] (b) (4) 202121 (Teva, this application), The most recent control documents regarding this drug product: #06-0827 for [redacted] (b) (4) (\\cdsnas\OGDS6\CONTROLS\2006-docs\06-0827.pdf). Per CC #06-0827, the DBE requests the following for this drug product: 1. A single-dose, two-way crossover fasting in-vivo bioequivalence study comparing Progesterone Capsules, 200 mg, to the reference listed drug (RLD), prometrium® Capsules, 200 mg. 2. A single-dose, two-way crossover fed in-vivo bioequivalence study comparing Progesterone Capsules, 200 mg, to the RLD. 3. Progesterone in plasma should be measured. The PK parameters should be determined based on both baseline-corrected and baseline-uncorrected plasma concentration data 4. Bioequivalence based on (90% CI): Progesterone There is no USP method for this product. Also there is no specific DBE-recommended dissolution test method currently available in the public or internal dissolution database on the Office of Generic Drugs website. The NDA dissolution method is considered unconventional and thus the method is not recommended for generic versions of Prometrium® Capsules. Instead the firm is recommended to develop its own dissolution method. The DBE is currently recommending the following method if the firm's method is not acceptable [DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive]: Media: 4.0 % of SLS Phosphate Buffer pH 6.8* Volume: 250 mL Temperature: 37 °C ± 0.5 °C USP Apparatus: III (Reciprocating Cylinder) Top Screen: 30 mesh Bottom Screen: 40 mesh Sinker: yes Speed: 30 dip/minute Sampling times 15, 30, 45 and 60 minutes or till 80% is dissolved. *To avoid excess foam formation, two drops of simethicone should be added. **Specification (as a reference):** NLT [redacted] (b) (4) (Q) of progesterone is dissolved in 45 minute

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	YES	1
Single-dose fed	YES	1
Steady-state	NO	--
In vitro dissolution	YES	2 (previously reviewed plus new data submitted here)
Waiver requests	YES	1 (100 mg)
BCS Waivers	NO	--
Clinical Endpoints	NO	--
Failed Studies	NO	--
Amendments	YES	1 (new dissolution data)

3.5 Pre-Study Bioanalytical Method Validation

Fasting Study Protocol No. 11036003:

Information Requested	Data
Bioanalytical method validation report location	Analytical Report, Appendix II
Analyte	Progesterone
Internal Standard (IS)	(b) (4)
Method description	An aliquot (0.500 mL) of human plasma (K_2EDTA) containing Progesterone was extracted using liquid-liquid extraction procedure combined with a derivatization step. The extracted samples were analyzed by a method in which liquid chromatography is combined with mass spectrometry.
Limit of quantitation	50.0 pg/mL
Average recovery of drug (%)	QC A: 85.1%, QC B: 88.4%, QC C: 82.6%
Average recovery of IS (%)	111.2%
Standard curve concentrations (pg/mL)	50.0 to 30000 pg/mL
QC concentrations (pg/mL)	QC LLOQ: 50.0 pg/mL, QC A: 150 pg/mL, QC B: 4500 pg/mL, QC C: 22500 pg/mL, QC ULOQ: 30000 pg/mL
QC Intraday precision range (%)	0.8% to 8.0%
QC Intraday accuracy range (%)	96.3% to 103.6%
QC Interday precision range (%)	2.9% to 10.7%
QC Interday accuracy range (%)	-9.4% to 1.8%
Short term stability (hrs)	26.3 hours @ room temperature
Stock stability (days)	29 days at a concentration of 100 mcg/mL when stored at -22±10°C in methanol for Progesterone 29 days at concentrations of 3000 ng/mL and 5.00 ng/mL when stored at -22±10°C in 50/50, v/v, methanol/water solution for Progesterone 113 days at a concentration of 100 mcg/mL when stored at -22±10°C in methanol for (b) (4)
Processed stability (hrs)	82.1 hours at room temperature
Freeze and thaw stability (cycles)	5 cycles at -22±10°C and -80±15°C
Long term storage stability (days)	176 days at -22±10°C and 22 days at -80±15°C
Dilution integrity	60000 pg/mL diluted 5 fold and 10 fold
Selectivity	Progesterone is endogenous, therefore a screening evaluation of human plasma from different donors to determine the endogenous level was performed. No interfering peak was noted for (b) (4) (IS) for lots tested.

Fed Study Protocol No. 3716:

Information Requested	Data
Bioanalytical method validation report location	Analytical Report, Appendix II
Analyte	Progesterone
Internal Standard (IS)	(b) (4)
Method description	An aliquot (0.500 mL) of human plasma (K_2EDTA) containing Progesterone was extracted using liquid-liquid extraction procedure combined with a derivatization step. The extracted samples were analyzed by a method in which liquid chromatography is combined with mass spectrometry.
Limit of quantitation	0.100 ng/mL
Average recovery of drug (%)	QC A: 90.2%, QC B: 92.5%, QC C: 92.5%
Average recovery of IS (%)	95.5%
Standard curve concentrations (ng/mL)	0.100 to 150 ng/mL
QC concentrations (ng/mL)	QC LLOQ: 0.100 ng/mL, QC A: 0.300 ng/mL, QC B: 22.5 ng/mL, QC C: 110 ng/mL, QC ULOQ: 150 ng/mL
QC Intraday precision range (%)	1.6% to 5.5%
QC Intraday accuracy range (%)	97.3% to 110.0%
QC Interday precision range (%)	3.0% to 10.2%
QC Interday accuracy range (%)	-1.3% to 0.4%
Short term stability (hrs)	26.7 hours @ room temperature
Stock stability (days)	29 days at a concentration of 100 mcg/mL when stored at -22±10°C in methanol for Progesterone 29 days and 20 days at concentrations of 5.00 ng/mL and 15000 ng/mL, respectively, when stored at -22±10°C in 50/50, v/v, methanol/water solution for Progesterone 113 days at a concentration of 100 mcg/mL when stored at -22±10°C in methanol for (b) (4)
Processed stability (hrs)	88.3 hours at room temperature
Freeze and thaw stability (cycles)	6 cycles at -22±10°C and -80±15°C
Long term storage stability (days)	124 days at -22±10°C and 15 days at -80±15°C
Dilution integrity	220 ng/mL diluted 2 fold and 4 fold 450 ng/mL diluted 5 fold and 10 fold 840 ng/mL diluted 10 fold and 12.5 fold
Selectivity	Progesterone is endogenous, therefore a screening evaluation of human plasma from different donors to determine the endogenous level was performed. No interfering peak was noted for (b) (4) (IS) for lots tested.

SOPs submitted	**SOP DH 2.10** (October 20, 2008): Preparation of Standards, Quality Control Samples and their Acceptance Criteria for Analytical Runs **SOP DH 6.9** (September 22, 2009): Archiving of Raw Data **SOP DH 8.5** (March 16, 2009): Coding of Study Samples, Calibration Standards, and Quality Control Samples, Selection of Repeats and Data Reporting **SOP DH 10.2** (August 31, 2009): Incurred Sample Reanalysis **SOP GP 15.6** (October 5, 2009): Baseline Integration and Chromatography Review **BAM 254.01** (September 29, 2009): Determination of Progesterone in Human Plasma by LC/MS/MS **BAM 255.02** (March 30, 2010) Determination of Progesterone in Human Plasma by LC/MS/MS
Was the % recovery consistent across QC concentrations?	YES
Is the same anticoagulant used in the pre-method validation study used in the sample assay?	YES (K_2EDTA)
If not, was cross validation study conducted?	N/A
Was the dilution factor adequate for the current study sample analysis?	YES
Was the same dilution medium (plasma/solvent) used during validation and sample analysis?	YES
Does the duration of the each of the stability parameters support the sample preparation and assay dates	YES
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	INADEQUATE (See Comments Below)

Comments on the Pre-Study Method Validation:

The reviewer notes that the average recovery of IS (%) for the validated method used in the fasting BE study was greater than 100% (111.2%). The firm will be asked to explain this result and discuss any impact on the results of the fasting BE study.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Progesterone – Fasting Study Protocol No. 11036003 (NOT Adjusted):

Study Ref. No.	Study Objective	Study Design	Treatments	Subjects	Mean Parameters ± SD (%CV)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUC0-t (pg·hr/mL)	AUC∞ (pg·hr/mL)	T½ (hr)	Kel (hr^{-1})	
Study # 11036003	Study title: A Study to Evaluate the Relative Bioavailability of a Test Formulation of Progesterone Soft Gelatin 200 mg capsules (TEVA Pharmaceuticals USA) Compared to Prometrium® (progesterone, USP) 200 mg Capsules (Solvay Pharmaceuticals) in Post Menopausal Females Under Fasting Conditions	Single-Dose, Randomized, Two-Treatment, Three-Period, Partial Replicate Design Crossover Study	**Test Product A:** Progesterone Soft Gelatin Capsules, 200 mg Oral TEVA Pharmaceuticals USA Batch No: 900464 Mfg. Date: 01/05/10 Exp. Date: 01/12	39 Healthy Female Subjects Mean Age: 55.41 ± 5.18 Range: 46 – 66	Mean = 6356.5897 ± 7544.1116 (118.6817)	Median: 2.00 Range: 1.0000-6.0000	Mean = 23000.7904 ± 26046.1926 (113.2404)	Mean = 30063.7823 ± 28817.6913 (95.8552)	Mean = 13.3792 ± 9.1197 (68.1631)	Mean = 0.0679 ± 0.0386 (56.8577)	Module 5.3.1.2
			Reference Product B: Prometrium® (progesterone, USP), 200 mg Capsules Oral Manufactured by: Catalent Pharma Solutions, Marketed by: Solvay Pharmaceuticals, Inc. Lot No: 500509 Exp. Date: AUG 2012		Mean = 6427.7662 ± 8360.4028 (130.0670)	Median: 2.00 Range: 1.0000-12.0000	Mean = 21567.7343 ± 22565.5789 (104.6266)	Mean = 29850.1795 ± 25597.9230 (85.7547)	Mean = 12.1024 ± 6.0663 (50.1249)	Mean = 0.0703 ± 0.0363 (51.5402)	

Baseline Adjusted Progesterone – Fasting Study Protocol No. 11036003:

Study Ref. No.	Study Objective	Study Design	Treatments	Subjects	Mean Parameters ± SD (%CV)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUC0-t (pg·hr/mL)	AUC∞ (pg·hr/mL)	T½ (hr)	Kel (hr^{-1})	
Study # 11036003	Study title: A Study to Evaluate the Relative Bioavailability of a Test Formulation of Progesterone Soft Gelatin 200 mg capsules (TEVA Pharmaceuticals USA) Compared to Prometrium® (progesterone, USP) 200 mg Capsules (Solvay Pharmaceuticals) in Post Menopausal Females Under Fasting Conditions	Single-Dose, Randomized, Two-Treatment, Three-Period, Partial Replicate Design Crossover Study	**Test Product A:** Progesterone Soft Gelatin Capsules, 200 mg Oral TEVA Pharmaceuticals USA Batch No: 900464 Mfg. Date: 01/05/10 Exp. Date: 01/12	39 Healthy Female Subjects Mean Age: 55.41 ± 5.18 Range: 46 – 66	Mean = 6329.5504 ± 7546.7918 (119.2311)	Median: 2.00 Range: 1.0000-6.0000	Mean = 22357.5034 ± 26145.0614 (116.9409)	Mean = 28929.6285 ± 28994.5696 (100.2245)	Mean = 11.0425 ± 9.4832 (85.8795)	Mean = 0.0965 ± 0.0792 (82.0234)	Module 5.3.1.2
			Reference Product B: Prometrium® (progesterone, USP), 200 mg Capsules Oral Manufactured by: Catalent Pharma Solutions, Marketed by: Solvay Pharmaceuticals, Inc. Lot No: 500509 Exp. Date: AUG 2012		Mean = 6403.3690 ± 8361.6140 (130.5815)	Median: 2.00 Range: 1.0000-12.0000	Mean = 20983.0607 ± 22592.0889 (107.6682)	Mean = 28332.8705 ± 25683.3711 (90.6487)	Mean = 10.3921 ± 6.2266 (59.9164)	Mean = 0.0899 ± 0.0572 (63.5946)	

Progesterone – Fed Study Protocol No. 3716 (NOT Adjusted):

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)*	AUC_{0-t} (ng·hr/mL)	AUC_{0-inf} (ng·hr/mL)	$T_{½}$ (hr)	λ_z (hr^{-1})	
Study # 3716	The objective of this study was to determine and compare the rate and extent of absorption of progesterone from a test formulation of Progesterone Soft Gelatin Capsules, 200 mg versus the reference Prometrium® 200 mg Capsules under fed conditions.	Randomized single-dose partial-replicate crossover	**Treatment A:** Progesterone Soft Gelatin Capsules, 200 mg p.o. [Batch #900464]	100 completing (100 F) healthy subjects 57.0 years (44 to 70 years)	18.07 (162.11)	3.50 (0.50 – 10.07)	43.27 (125.19)	49.97 (119.49) ♠	5.91 (22.98) ♠	1.17E-01 (3.09E+01) ♠	Module 5.3.1.2
					First Administration						
			Treatment B: Prometrium® 200 mg Capsules p.o. [Lot #500509]		19.64 (144.66)	3.51 (1.00 – 10.02)	46.26 (114.67)	60.35 (103.81) ♦	6.11 (24.74) ♦	1.13E-01 (3.11E+01) ♦	
					Second Administration						
					17.59 (215.49)	4.02 (0.50 – 10.07)	43.93 (142.44)	54.39 (130.64) ♪	5.79 (26.07) ♪	1.20E-01 (4.94E+01) ♪	

* median (range) ♠ n=86 ♦ n=73 ♪ n=64

Baseline Adjusted Progesterone - Fed Study Protocol No. 3716:

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects [No. (M/F)] Type Age: mean (Range)	Mean Parameters (%CV)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)*	AUC_{0-t} (ng·hr/mL)	AUC_{0-inf} (ng·hr/mL)	$T_{½}$ (hr)	λ_z (hr^{-1})	
Study # 3716	The objective of this study was to determine and compare the rate and extent of absorption of progesterone from a test formulation of Progesterone Soft Gelatin Capsules, 200 mg versus the reference Prometrium® 200 mg Capsules under fed conditions.	Randomized single-dose partial-replicate crossover	**Treatment A:** Progesterone Soft Gelatin Capsules, 200 mg p.o. [Batch #900464]	100 completing (100 F) healthy subjects 57.0 years (44 to 70 years)	18.00 (162.31)	3.50 (0.50 – 10.07)	42.57 (126.83)	49.64 (119.97) ♠	5.70 (23.14) ♠	1.22E-01 (3.00E+01) ♠	Module 5.3.1.2
					First Administration						
			Treatment B: Prometrium® 200 mg Capsules p.o. [Lot #500509]		19.63 (144.69)	3.51 (1.00 – 10.02)	45.98 (115.05)	59.36 (104.72) ♣	5.93 (24.62) ♣	1.17E-01 (3.27E+01) ♣	
					Second Administration						
					17.57 (215.63)	4.02 (0.50 – 10.07)	43.54 (136.39)	53.67 (131.42) ♥	5.67 (26.74) ♥	1.22E-01 (4.92E+01) ♥	

* median (range) ♠ n=86 ♣ n=74 ♥ n=65

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Progesterone Capsule 200 mg (1 x 200 mg) Fasting BE Study No. 11036003, n = 39 (all post-menopausal females) Summary of Statistical Analysis – Unscaled Data Least Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
AUC0-t (hr *pg/ml)	13956.97	13882.05	1.01	89.96	112.36
AUC∞ (hr *pg/ml)	18080.84	17752.97	1.02	88.93	116.64
Cmax (pg/ml)	3568.13	3672.89	0.97	84.45	111.75

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (hr *pg/ml)	1.01	89.96	112.36	0.1453518	0.3812504	-0.08159	Scaled/PE	PASS
AUC∞ (hr *pg/ml)	1.05	88.93	116.64	0.1680042	0.4098831	-0.072659	Scaled/PE	PASS
Cmax (pg/ml)	0.97	84.45	111.75	0.1750762	0.418421	-0.092164	Scaled/PE	PASS

Progesterone Capsule 200 mg (1 x 200 mg) Fed BE Study No. 3716, n = 100 (all post-menopausal females) Summary of Statistical Analysis – Unscaled Data Least Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Geometric Means			90% CI	
Parameter	Test	Reference	T/R Ratio	Lower CI	Upper CI
LAUCT	42.56	44.66	0.95	86.49	104.97
LCMAX	18.01	18.54	0.97	83.47	113.12

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (ng·hr/mL)	0.95	86.49	104.97	0.4338851	0.6586996	-0.274693	Scaled/PE	PASS
AUC∞ (ng·hr/mL)	0.90	.	.	0.4488096	0.6699325	-0.246303	Scaled/PE	PASS
Cmax (ng/mL)	0.97	83.47	113.12	1.0730172	1.0358654	-0.688154	Scaled/PE	PASS

Table 3. Reanalysis of Study Samples

Study No. 11036003 (Revision 0) Progesterone								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays[2]		Actual number		% of total assays[2]	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
AAR	2	5	0.1	0.2	2	5	0.1	0.2
IA	3	4	0.1	0.2	3	4	0.1	0.2
IISR	7	4	0.3	0.2	7	4	0.3	0.2
UC	3	11	0.1	0.5	3	11	0.1	0.5
Total	15	24	0.6	1.0	15	24	0.6	1.0

Total number of samples analyzed = 2339

Study No. 3716 (Version 2.0, Amendment 1) Progesterone								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays[2]		Actual number		% of total assays[2]	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.0	0.0	0	0	0.0	0.0
AAR	5	12	0.1	0.2	5	12	0.1	0.2
BAR	26	66	0.4	1.1	26	66	0.4	1.1
IA	2	6	0.0	0.1	2	6	0.0	0.1
IISR	7	22	0.1	0.4	7	22	0.1	0.4
UC	5	12	0.1	0.2	5	12	0.1	0.2
Total	45	118	0.8	2.0	45	118	0.8	2.0

Total number of samples analyzed = 5992

AAR – Sample Concentration Above Acceptance Range
BAR – Sample Concentration Below Acceptance Range
IA – Incomplete Analysis
IISR – Inconsistent Internal Standard Response
UC – Unacceptable Chromatography
Note: When a sample was repeated more than once, only the first repeat code assigned was included in the calculation in order to adequately represent the total number of samples analyzed.

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0".
[2] The % of total assays is calculated by dividing the actual number by the total number of samples analyzed

Reanalysis SOPs submitted?	YES
Do you agree with the reassay criteria**: analytical and pharmacokinetic**	YES
If not, list the criteria that you don't agree and provide additional comment below	N/A
Are the data in the summary table consistent with the data in the full analytical report?	Fasting: YES Fed: NO
If not, provide comment below	See Comments Below
Did reviewer reanalyze study results?	NO
Was the study outcome changed based on reviewer reanalysis?	N/A
Did the firm provide a comprehensive table of repeat samples in the format recommended by the DBE?	Fasting: YES Fed: NO
Did the firm provide numerical raw data (e.g. peak height, peak area, response count of IS and analyte) in run sequence order (i.e. Run log)?	Fasting: YES Fed: NO

Comments from the Reviewer:

FASTING:
For the fasting study, the total number of repeated samples was 1.7% (39/2339). Seven (7) of these were repeated as "above acceptable range" (AAR) following first analysis since the concentrations obtained were above the analytical range used during the study. These samples were diluted two-fold along with QC samples. Per the pre-study method validation report, dilution integrity of up to 60,000 pg/mL was demonstrated. These repeats for AAR are acceptable.

There were 14 samples re-assayed in the fasting study due to "unacceptable chromatography" (UC). Two (2) of these 14 unacceptable chromatograms were submitted in the 20% representative chromatograms. The reviewer agrees with the firm's conclusion that those two chromatograms were unacceptable (due to peak splitting). Because of other deficiencies with regard to reanalysis of subject samples, this reviewer will request the chromatograms for the other 12 subject samples flagged as UC.

The reviewer spot-checked in the "Analyst" spreadsheets that the subject samples reanalyzed due to "inconsistent internal standard response" (IISR). The reviewer found no discrepencies, and these reassays are acceptable (adequate).

FED:
With regard to the fed BE study, the firm did not submit the following:

1. "Analyst" spreadsheet with all of the data for both the analyte and the internal standard for the entire study.
2. 20% representative chromatograms
3. Complete Analytical Report (the analytical report submitted did not include the "Summary of Repeats for Analytical Reasons and Reassay for Progesterone in Human Plasma" Table).

Because of these missing items, this reviewer was unable to validate that the reanalysis of subject samples for the fed BE study are acceptable by the DBE.

The firm will be asked to submit the aforementioned missing items for review. The reanalysis data are incomplete (inadequate) at this time.

3.7 Formulation

Location in appendix	Section 4.2
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive
Source of Method (USP, FDA or Firm)	FDA (not in database)
Medium	4% SLS in pH 6.8 Phosphate Buffer Add 2 drops of Simethicone to avoid excessive foam formation.
Volume (mL)	250 mL
USP Apparatus type	USP Apparatus III (Bio-Disc / Reciprocating Cylinder)
Top Screen	30 mesh
Bottom Screen	40 mesh
Speed	30 dip/minute
Temperature	37 °C ± 0.5 °C
Sinker	yes
Sampling Times	15, 30, 45 and 60 minutes or till 80% is dissolved
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Immediate release product
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
N/A			

Dissolution Amendment:
There is a "dissolution only" review which can be found in DARRTS [see in DARRTS for ANDA #202121 DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive]. The dissolution testing was deemed unacceptable because the proposed method demonstrated slow dissolution profiles for both the test and reference products (6-8 hours to achieve complete dissolution of this immediate release product). The firm was asked to develop a new dissolution method which is more representative of the IR formulation. As a suggestion, the DBE recommended the following dissolution method used in ANDA (b) (4) [see in DARRTS for ANDA (b) (4) LU, FANG 06/11/2010 N/A 06/11/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Not Applicable) Archive].

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Sampling times:	15, 30, 45 and 60 minutes or till 80% is dissolved.

*To avoid excess foam formation, two drops of simethicone should be added.

In an amendment dated 03/03/2011, Teva responded to the "dissolution only" review deficiency letter by submitting new comparative dissolution data using the aforementioned method. The results are more representative of the IR formulation (see section 4.3 below for details). That is, within an hour, the capsules are at or near complete dissolution for both strengths of the test product.

In similar ANDA (b) (4) the DBE-recommended specification for this product using the same dissolution method is *NLT* (b) (4) *(Q) dissolved in 45 minutes*. For this current ANDA, the reference product at both strengths meets this specification of *NLT* (b) (4) *(Q) in 45 minutes*. However, the test product does NOT meet this specification for the 100 mg strength (although it does meet for the 200 mg strength). There are two 100 mg capsules which were only (b) (4) dissolved at 45 minutes. Therefore, based on the data, this reviewer recommends a specification of ***NLT*** (b) (4) ***(Q) dissolved in 45 minutes***. For consistency, this specification is recommended for both strengths (100 mg and 200 mg). This recommended specification is the same as the specification proposed by Teva.

The DBE acknowledges that Teva will conduct the dissolution testing using DBE-recommended method with the following specification: NLT (b) (4) (Q) of progesterone is dissolved in 45 minutes. The dissolution study is acceptable (adequate).

3.9 Waiver Request(s)

Strengths for which waivers are requested, if applicable[7]	100 mg
Waiver regulation cited?	YES
Proportional to strength tested *in vivo*?	YES
Is dissolution acceptable?	YES
Waivers granted?	**WAIVER DENIED**
If not then why?	Incomplete (inadequate) fasting and fed BE studies

3.10 Deficiency Comments

1. The reviewer notes that the average recovery of IS (%) for the validated method used in the fasting BE study was greater than 100% (111.2%). The firm will be asked to explain this result and discuss any impact on the results of the fasting BE study.

2. The firm should submit the chromatograms for all subject samples from the fasting and fed BE studies flagged as unacceptable chromatography (UC).

3. The firm should submit "Analyst" spreadsheet with all of the data for both the analyte and the internal standard for the entire fed BE study.

4. The firm should submit 20% of chromatograms from the fed BE study (in addition to the chromatograms flagged as UC).

5. The firm should submit the -1, -0.5 and 0 hour data for the fed BE study.

[7] For Modified Release Dosage Forms, please note waiver is not applicable

3.11 Recommendations

1. The Division of Bioequivalence (DBE) finds the fasting bioequivalence study #11036003 conducted by Teva Pharmaceuticals on its Progesterone Capsule, 200 mg (Lot # 0001019502) comparing it to the reference product, Abbott's Prometrium® (Progesterone, USP) 200 mg Capsules (Lot # 500509), **incomplete (inadequate)** due to the deficiencies listed above.

2. The Division of Bioequivalence (DBE) finds the fed bioequivalence study #3716 conducted by Teva Pharmaceuticals on its Progesterone Capsule, 200 mg (Lot # 0001019502) comparing it to the reference product, Abbott's Prometrium® (Progesterone, USP) 200 mg Capsules (Lot # 500509), **incomplete (inadequate)** due to the deficiencies listed above.

3. The firm's dissolution testing on its Progesterone Capsule, 200 mg (Lot #0001019502, and 100 mg (Lot #0001019501) compared to the reference product, Abbott.'s Prometrium® (Progesterone, USP) 200 mg Capsules (Lot #500509) and 100 mg (Lot #500309) is **acceptable (adequate)**. The DBE acknowledges that the firm will conduct the dissolution testing using the following dissolution method and specification:

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Sampling times:	15, 30, 45 and 60 minutes or till 80% is dissolved.

*To avoid excess foam formation, two drops of simethicone should be added.

Specification: NLT (b) (4) (Q) dissolved in 45 minutes

4. Since the fasting and fed BE studies are incomplete (inadequate) at this time, the request for a waiver of the *in vivo* bioequivalence testing requirement for the 100 mg Test products under 21 CFR 320.22(d)(2) is not granted.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
None	--

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	11036003
Study Title	A Study to Evaluate the Relative Bioavailability of a Test Formulation of Progesterone Soft Gelatin 200 mg capsules (TEVA Pharmaceuticals USA) Compared to Prometrium® (progesterone, USP) 200 mg Capsules (Solvay Pharmaceuticals) in Post Menopausal Females Under Fasting Conditions
Clinical Site (Name, Address, Phone #)	Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739
Principal Investigator	Darin B. Brimhall, D.O., FACP, CPI
Dosing Dates	Period I: 02/20/10 Period II: 02/27/10 Period III: 03/06/10
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	March 11, 2010 to March 19, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	27 days at a temperature of -22±10°C

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Progesterone Capsules	PROMETRIUM® (progesterone, USP) Capsules
Manufacturer	Catalent Pharma. Solutions, LLC for TEVA Pharmaceuticals, USA	Unimed Pharma LLC Solvay Pharmaceuticals
Batch/Lot No.	Catalent Lot No: 1038900 Teva Batch No.: 0001019502 Packaging Lot No. 900464	500509
Manufacture Date	01/05/2010	N/A
Expiration Date	N/A	Aug 2012
Strength	200 mg	200 mg
Dosage Form	Soft Gelatin Capsule	Soft Gelatin Capsule
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (%)	98.5	98.7
Content Uniformity (mean, %CV)	Mean: 99.3 %CV: 0.6%	Mean: 98.3 %CV: 0.7%
Dose Administered	200 mg	200 mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	41 Enrolled / 41 Dosed / 39 Analyzed
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	**ABB:** 01, 05, 08, 10, 15, 18, 21, 22, 25, 30, 31, 35, 39, 42 **BBA:** 02, 04, 07, 12, 13, 16, 20, 23, 26, 29, 32, 34, 38, 40 **BAB:** 03, 06, 09, 11, 14, 17, 19, 24, 27, 28, 33, 36, 37, 41
Blood Sampling Times	In each period, 6 mL venous blood was collected in pre-chilled **K2 EDTA** vacutainers at the following nominal times: -1, -0.5, pre-dose (0 within 10 minutes of dosing), and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 18, and 24 hours.
Blood Volume Collected/Sample	6 mL collections (K2 EDTA vacutainers) X 19 = 114 mL X 3 periods = 342 mL + 55 mL (labs) = **397 mL**

Blood Sample Processing/Storage	After collection, the samples were gently inverted several times to ensure complete mixing and kept in an ice-water bath until being placed in the centrifuge and spun at high speed (2700-3000 rpm) for 10 minutes at 4°C. The resulting plasma was returned to the ice-water bath until separated into two approximately equal aliquots in appropriately labeled polypropylene screw-cap tubes and placed in the freezer (upright) until analysis. The time from blood collection until the plasma was placed in the freezer did not exceed 90 minutes. All plasma samples were stored frozen to at least -20°C.
IRB Approval	Approved 02/09/2010
Informed Consent	YES
Length of Fasting	All subjects began fasting for at least 10 hours prior to dosing. Subjects continued to fast until 4 hours post dosing.
Length of Confinement	In each period, the subjects reported to the clinical facility for check-in (Day -1) at least 10 hours prior to dosing. The subjects were released from the clinical facility approximately 24 hours after dosing in each study period.
Safety Monitoring	Vital signs (including scheduled blood pressure and pulse rate measurements), diagnostic tests were performed at the times specified in the protocol.

Comments on Study Design:

- Any subject that had a pre-dose concentration greater than 5% Cmax is included in the analysis as progesterone is an endogenous compound.

- Post-dose blood samples were baseline Adjusted for each period by deducting the mean of the three pre-dose values [-1.0, -0.5 and 0 hour (within 10 minutes of dosing) sample] from all post dose values. After baseline correction, any plasma concentration which was a negative value was set to zero (0.00) for PK analysis.

- The study design is acceptable (adequate).

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasted Study No. 11036003		
		Treatment Groups
		Test and Reference Products N = 39
Age (years)	Mean ± SD	55.41 ± 5.18
	Range	46 – 66
Age Groups	< 18	0 (0.00%)
	18 – 40	0 (0.00%)
	41 – 64	37 (94.87%)
	65 – 75	2 (5.13%)
	> 75	0 (0.00%)
Sex	Male	0 (0.00%)
	Female	39 (100.00%)
Ethnicity	Hispanic/Latino	7 (17.95%)
	Not Hispanic/Latino	32 (82.05%)
Race	American Indian/Alaskan Native	0 (0.00%)
	Asian	5 (12.82%)
	Black or African American	13 (33.33%)
	Native Hawaiian/Other Pacific Islander	0 (0.00%)
	White	13 (33.33%)
	Other	8 (20.51%)
Weight (lbs)	Mean ± SD	152.36 ± 27.40
	Range	112 – 209
Other Factors		
BMI (kg/m^2)	Mean ± SD	26.37 ± 3.37
	Range	19.7 – 31.7
Tobacco Users	Yes	0 (0.00%)
	No	39 (100.00%)

All post-menopausal female subjects were used in the BE study.

Table 8. Dropout Information, Fasting Bioequivalence Study

Fasted Study No. 11036003				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
04 (b) (6)	Noncompliance (positive alcohol test) Discontinued at Period III (Test: A)check-in	II	No	N/A
41 (b) (6)	Voluntary Withdrawal (no show) Withdrew at Period II check-in	I	No	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Fasted Bioequivalence Study Study No. 11036003	
	Test A (N %)	Reference B (N %)
Eye Disorders		
Eye Pruritus	0 (0.00%)	1 (2.44%)
Gastrointestinal Disorders		
Abdominal distension	1 (2.56%)	0 (0.00%)
Nausea	4 (10.26%)	1 (2.44%)
Vomiting	1 (2.56%)	0 (0.00%)
General Disorders and Administration Site Conditions		
Chest discomfort	0 (0.00%)	1 (2.44%)
Hot flush	1 (2.56%)	3 (7.32%)
Injury, Poisoning, and Procedural Complications		
Periorbital haematoma	0 (0.00%)	1 (2.44%)
Investigations		
Blood pressure increased	2 (5.13%)	3 (7.32%)
Body temperature increased	1 (2.56%)	0 (0.00%)
Haematology test abnormal	1 (2.56%)	0 (0.00%)
Musculoskeletal and Connective Tissue Disorders		
Myalgia	1 (2.56%)	0 (0.00%)
Nervous System Disorders		
Dizziness	0 (0.00%)	1 (2.44%)
Headache	3 (7.69%)	8 (19.51%)
Psychiatric Disorders		
Crying	0 (0.00%)	1 (2.44%)
Renal and Urinary Disorders		
Pollakiuria	1 (2.56%)	0 (0.00%)
Reproductive System and Breast Disorders		
Breast tenderness	1 (2.56%)	1 (2.44%)
Libido increased	0 (0.00%)	1 (2.44%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0 (0.00%)	2 (4.88%)
Nasal congestion	1 (2.56%)	1 (2.44%)
Skin and Subcutaneous Tissue Disorders		
Swelling face	0 (0.00%)	1 (2.44%)
Total	**13 (33.33%)**	**15 (36.59%)**

N% = Number of subjects reporting AE / number of subjects dosed with respective study drug at least once (x 100)
Total N% = Number of subjects that reported at least one AE / number of subjects dosed with respective study drug at least once (x100)
Test: 39 subjects dosed, Reference: 41 subjects dosed at least once

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Fasted Study No. 11036003		
Type	**Subject #s (Test A)**	**Subject #s (Reference B)**
Caffeine consumption	N/A	30 (b) (6) 40

Comments on Dropouts/Adverse Events/Protocol Deviations:

- The single subject (#40) that vomited was not dropped because the emesis occurred nearly 24 hours after dosing (emesis on 03/07/2010 at 7:45 AM, and dosing was on 03/06/2010 at approximately 7:45 AM). This reviewer agrees with the handling of subject #40 data.

- The reviewer finds the handling of adverse events/protocol deviations as acceptable (adequate).

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. 11036003 (Revision 0) Progesterone										
Parameter	**Standard Curve Samples**									
Concentration (pg/mL)	50.0	100	300	1200	3000	6000	12000	18000	27000	30000
Inter day Precision (%CV)	2.3	4.8	2.4	3.4	2.0	1.7	1.8	1.8	2.6	4.0
Inter day Accuracy (%Bias)	-0.4	1.0	0.0	0.0	0.3	1.2	0.8	-0.6	-1.5	-0.7
Linearity	0.9970 to 0.9996									
Linearity Range (pg/mL)	50.0 to 30000									
Sensitivity/LOQ (pg/mL)	50.0									

Bioequivalence Study No. 11036003 (Revision 0) Progesterone				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150	2250	9000	22500
Inter day Precision (%CV)	5.2	2.3	2.4	2.0
Inter day Accuracy (%Bias)	-2.7	0.0	0.6	-1.3

Comments on Study Assay Validation:

Acceptable (adequate)

Any interfering peaks in chromatograms?	NO
Were 20% of chromatograms included?	YES
Were chromatograms serially or randomly selected?	Serial Batch #s 03CIO, 04CIO, 06CIO, and 07CIO (subject #s 01 – 09)

Comments on Chromatograms:

Acceptable (Adequate)

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
DH 8.5	March 16, 2009	Coding of Study Samples, Calibration Standards and Quality Control Samples, Selection of Repeats and Data Reporting

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays:

According to the report, "*As per sponsor's request, an incurred sample re-analysis evaluation was performed for Progesterone. Two samples / subject / period (one at or near the Cmax / Tmax timepoint and one at elimination phase timepoint, for each period) were selected and analyzed. In this study, 162 samples ((b) (4) for the first (b) (4) samples and (b) (4) for the (b) (4) remaining samples) were analyzed as part of the incurred sample re-analysis evaluation. Four study samples were flagged as IISR (Inconsistent Internal Standard Response) and two study samples were flagged as IA (Incomplete Analysis). These samples were not included in the ISR (Incurred Samples Re-analysis) evaluation. All 156 remaining samples were within ±20.0% of the mean of the original result and ISR result, allowing us to conclude with confidence that the method was performed as validated and is reproducible.*"

The firm will be asked to submit all chromatograms for subject samples reassayed due to "unacceptable chromatogram".

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Not Adjusted for Baseline Progesterone Levels:

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT	pg hr/mL	23002.92	113.25	21833.59	107.77	21812.85	99.93	1.05	1.05	1.00
AUCI	pg hr/mL	30152.84	95.47	29839.83	90.72	30420.46	79.66	1.01	0.99	0.98
CMAX	pg/mL	6356.590	118.68	6242.923	129.65	6752.923	128.18	1.02	0.94	0.92
TMAX	hr	2.000	.	2.000	.	2.500	.	1.00	0.80	0.80
KE	hr-1	0.068	56.94	0.072	53.21	0.070	48.37	0.95	0.98	1.03
THALF	hr	13.900	83.27	11 376	37.09	12.663	60.40	1.22	1.10	0.90

* Tmax values are presented as median, range

Baseline Adjusted:

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT	pg hr/mL	22359.72	116.95	21321.54	110.13	21147.16	103.55	1.05	1.06	1.01
AUCI	pg hr/mL	28997.69	99.93	28737.79	94.07	28466.15	85.96	1.01	1.02	1.01
CMAX	pg/mL	6329.550	119.23	6221.740	130.09	6724.963	128.75	1.02	0.94	0.93
TMAX	hr	2.000	.	2.000	.	2.500	.	1.00	0.80	0.80
KE	hr-1	0.097	81.27	0.088	53.84	0.092	70.80	1.11	1.06	0.96
THALF	hr	11.385	103.87	9 519	40.72	11.161	70.44	1.20	1.02	0.85

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Baseline Adjusted – Fasting Study Protocol No. 11036003

Progesterone Gelatin Capsules, 200 mg versus Prometrium® (progesterone, USP) 200 mg Capsules
Dose (1 x 200 mg Capsule)
Geometric Means, Ratio of Means, 90% Confidence Intervals, Reference %CV, Sigma wr, 95% Upper Confidence Bound
Based on ANOVA of Ln-Transformed Data

Fasted Bioequivalence Study (Study No. 11036003)

Analyte: Progesterone (Baseline Adjusted)

Parameter	Ratio	Reference % CV*	Sigma wr	95% Upper Confidence Bound**
AUC0-t	1.0087	40.13	0.3865	-0.0832
AUC∞	1.0338	43.95	0.4202	-0.0832
Cmax	0.9751	44.35	0.4238	-0.0952

N=39 for AUC0-t and Cmax; N=30 for AUC0-inf for Test Product A.
N=77 for AUC0-t and Cmax; N=54 for AUC0-inf for Reference Product B.
* Intrasubject variability for Reference Product B (sqrt(exp(MSEref)-1) x 100%).
** Bioequivalent if 95% upper confidence bound for $(\mu T-\mu R)^2- \theta(s^2_{wr}) \leq 0$ and the geometric mean ratios (T/R) fall within the limits of 0.80-1.25. Sigma wr = sqrt(MSEref)

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Not Adjusted for Baseline Progesterone Levels:

Progesterone Capsule
200 mg (1 x 200 mg)
Fasting BE Study No. 11036003, n = 39 (all post-menopausal females)
Summary of Statistical Analysis – Unscaled Data
Least Square Geometric Means, Point Estimates and 90% Confidence Intervals

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
AUC0-t (hr *pg/ml)	15053.29	14677.81	1.03	92.23	114.04
AUC∞ (hr *pg/ml)	19703.63	19386.82	1.02	89.52	115.38
Cmax (pg/ml)	3619.10	3712.97	0.97	84.82	112.01

Scaled Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (hr *pg/ml)	1.03	92.23	114.04	0.1318649	0.363132	-0.071161	Scaled/PE	PASS
AUC∞ (hr *pg/ml)	1.05	89.52	115.38	0.1449815	0.3807643	-0.059681	Scaled/PE	PASS
Cmax (pg/ml)	0.97	84.82	112.01	0.1720749	0.4148191	-0.091252	Scaled/PE	PASS

Baseline Adjusted:

Progesterone Capsule
200 mg (1 x 200 mg)
Fasting BE Study No. 11036003, n = 39 (all post-menopausal females)
Summary of Statistical Analysis – Unscaled Data
Least Square Geometric Means, Point Estimates and 90% Confidence Intervals

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
AUC0-t (hr *pg/ml)	13956.97	13882.05	1.01	89.96	112.36
AUC∞ (hr *pg/ml)	18080.84	17752.97	1.02	88.93	116.64
Cmax (pg/ml)	3568.13	3672.89	0.97	84.45	111.75

Scaled Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (hr *pg/ml)	1.01	89.96	112.36	0.1453518	0.3812504	-0.08159	Scaled/PE	PASS

Scaled Data								
Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC∞ (hr *pg/ml)	1.05	88.93	116.64	0.1680042	0.4098831	-0.072659	Scaled/PE	PASS
Cmax (pg/ml)	0.97	84.45	111.75	0.1750762	0.418421	-0.092164	Scaled/PE	PASS

Table 17. Additional Study Information, Fasting Study

Not Adjusted for Baseline Progesterone Levels:

	Test	Reference 1	Reference 2
Kel and AUC∞ determined for how many subjects?	30	27	27
Do you agree or disagree with firm's decision?	AGREE	AGREE	AGREE
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	N/A**	N/A	N/A
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	No	No	No

** Progesterone is endogenous hormone.

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	30	0.88	0.53	0.97
Reference 1	27	0.91	0.76	0.98
Reference 2	27	0.90	0.71	0.97

Baseline Adjusted:

	Test	Reference 1	Reference 2
Kel and AUC∞ determined for how many subjects?	30	27	28
Do you agree or disagree with firm's decision?	AGREE	AGREE	AGREE
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	N/A**	N/A	N/A
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	No	No	No

** Progesterone is endogenous hormone.

Treatment	n	Mean	Minimum	Maximum
Test	30	0.91	0.53	1.00
Reference 1	27	0.93	0.83	1.00
Reference 2	28	0.92	0.71	1.00

Comments on Pharmacokinetic and Statistical Analysis:

The reviewer used the SAS code "Continu2" in order to verify the firm's statistical analysis.

Statistical analysis was carried out both on baseline adjusted (subtract mean of -1, -.5 and 0 hour predose concentrations) and unadjusted plasma concentrations. The reviewer notes that many of the baseline measurements were below the limit of quantitation, and therefore listed as zero (0). Therefore, baseline adjustment results are not that different from the unadjusted results. The reason for the low baseline in these subjects was that the subjects were all post-menopausal women.

The test product meets bioequivalence criteria using either the unscaled or reference scaled average approach (based on reviewer's calculations).

The median Tmax values calculated by the reviewer for progesterone are similar between test and reference products (Test: 2 hours; Reference: 2 and 2.5 hours for ref 1 and ref 2 dosing, respectively).

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The firm's *in vivo* BE study under fasting condition is **incomplete (inadequate)** due to the deficiencies listed in Deficiency Comments Section of this review.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Not Adjusted for Baseline Progesterone Levels:

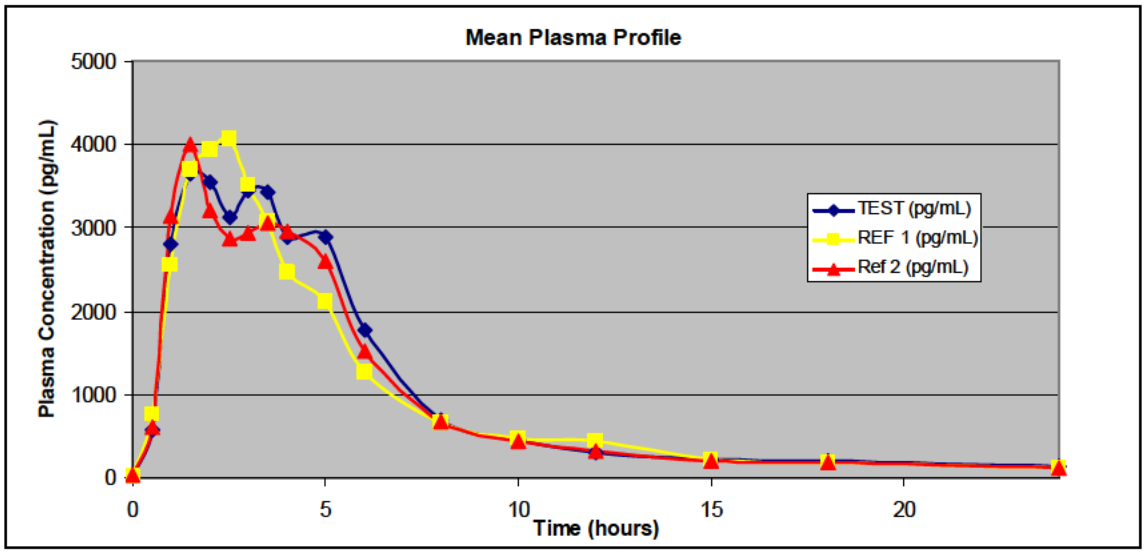
	Test (n=39)		Reference 1 (n=39)		Reference 2 (n=39)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	27.09	140.03	21.19	137.96	27.99	180.32	1.28	0.97	0.76
0.50	572.97	144.28	759.66	255.31	605.69	233.64	0.75	0.95	1.25
1.00	2801.88	147.47	2544.03	123.24	3148.47	204.19	1.10	0.89	0.81
1.50	3652.07	143.06	3697.64	148.39	4004.36	186.28	0.99	0.91	0.92
2.00	3542.62	137.09	3929.51	167.92	3203.79	156.19	0.90	1.11	1.23
2.50	3118.77	131.40	4076.33	176.77	2864.44	120.49	0.77	1.09	1.42
3.00	3453.00	157.47	3516.05	173.02	2932.67	108.47	0.98	1.18	1.20
3.50	3422.97	174.42	3077.05	149.59	3052.46	122.50	1.11	1.12	1.01
4.00	2892.62	167.73	2459.64	128.75	2952.69	161.01	1.18	0.98	0.83
5.00	2894.90	139.55	2115.33	95.95	2605.78	126.87	1.37	1.11	0.81
6.00	1770.31	149.84	1265.38	117.19	1518.07	115.64	1.40	1.17	0.83
8.00	684.26	118.92	657.87	105.81	680.13	103.73	1.04	1.01	0.97
10.00	456.31	127.97	480.79	181.57	439.66	82.87	0.95	1.04	1.09
12.00	300.49	106.41	445.20	305.31	316.41	100.12	0.67	0.95	1.41
15.00	225.98	109.98	212.01	151.07	203.43	90.11	1.07	1.11	1.04
18.00	199.81	85.29	177.66	80.27	177.78	75.85	1.12	1.12	1.00
24.00	129.75	71.83	118.28	76.24	125.33	73.58	1.10	1.04	0.94

Baseline Adjusted:

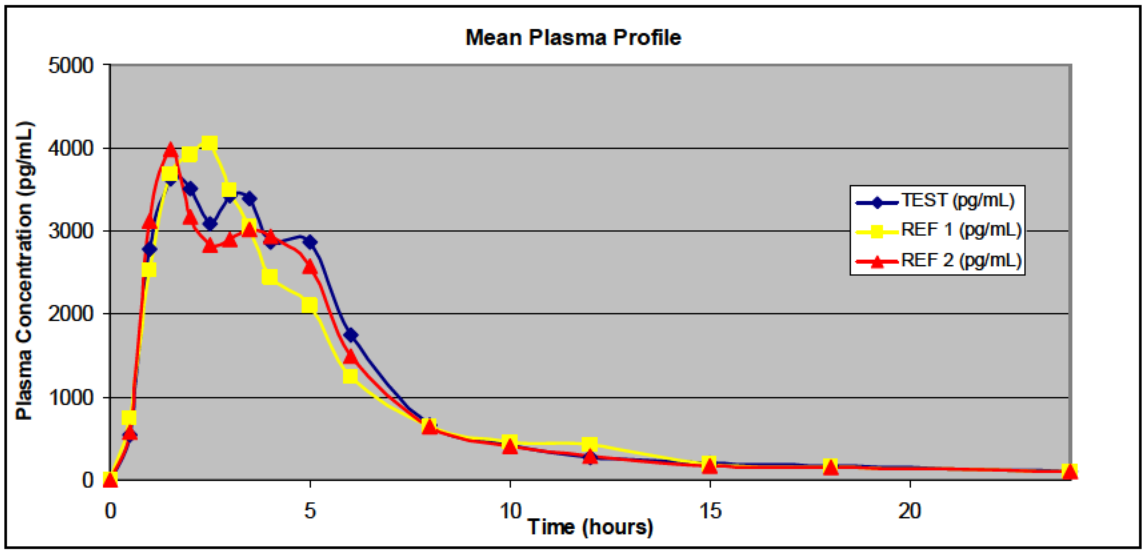
	Test (n=39)		Reference 1 (n=39)		Reference 2 (n=39)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00	.	.	.	.
0.50	547.95	151.93	739.97	261.46	580.12	244.67	0.74	0.94	1.28
1.00	2774.85	149.04	2522.84	124.06	3120.51	206.13	1.10	0.89	0.81
1.50	3625.03	144.04	3676.46	149.19	3976.40	187.50	0.99	0.91	0.92
2.00	3515.58	137.95	3908.33	168.86	3175.83	157.47	0.90	1.11	1.23
2.50	3091.73	132.38	4055.15	177.72	2836.48	121.67	0.76	1.09	1.43
3.00	3425.96	158.77	3494.87	174.07	2904.71	109.65	0.98	1.18	1.20
3.50	3395.94	175.96	3055.87	150.64	3024.50	123.89	1.11	1.12	1.01
4.00	2865.58	169.53	2438.46	129.89	2924.73	162.84	1.18	0.98	0.83
5.00	2867.86	141.10	2094.15	96.77	2577.82	128.55	1.37	1.11	0.81
6.00	1743.27	152.53	1244.20	118.81	1490.11	118.37	1.40	1.17	0.83
8.00	657.22	124.87	636.69	108.94	652.17	109.09	1.03	1.01	0.98
10.00	429.27	137.53	459.60	189.05	412.18	88.07	0.93	1.04	1.12
12.00	273.45	120.00	424.02	319.81	288.93	108.62	0.64	0.95	1.47
15.00	199.19	128.35	190.83	166.53	176.09	103.30	1.04	1.13	1.08
18.00	173.42	102.19	156.48	90.12	150.48	89.11	1.11	1.15	1.04
24.00	103.14	98.74	97.21	92.39	98.07	87.71	1.06	1.05	0.99

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Not Adjusted for Baseline Progesterone Levels:



Baseline Adjusted:



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	3716
Study Title	A Three-Way Crossover, Partial Replicate, Open-Label, Single-Dose, Fed, Relative Bioavailability Study of Progesterone Soft Gelatin Capsules, 200 mg Versus Prometrium® 200 mg Capsules in Normal, Healthy, Non-Smoking Post-Menopausal and/or Surgically Sterile Female Subjects
Clinical Site (Name, Address, Phone #)	Biovail Contract Research (a Division of Biovail Corporation) 460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6 Telephone: (416) 752-3636 / (416) 686-6334 Fax: (416) 752-7610 / (416) 690-1880
Principal Investigator	Pierre Geoffroy, M.D. C.M., M.Sc., F.C.F.P.
Dosing Dates	**Group 1** Period I: February 14, 2010 Period II: February 21, 2010 Period III: February 28, 2010 **Group 2** Period I: March 6, 2010 Period II: March 13, 2010 Period III: March 20, 2010
Analytical Site (Name, Address, Phone #)	(b) (4)
Analytical Dates	April 2, 2010 to May 12, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	87 days at a temperature of -22±10°C

Table 20. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Progesterone Capsules	PROMETRIUM® (progesterone, USP) Capsules
Manufacturer	Catalent Pharma. Solutions, LLC for TEVA Pharmaceuticals, USA	Unimed Pharma LLC Solvay Pharmaceuticals
Batch/Lot No.	Catalent Lot No: 1038900 Teva Batch No.: 0001019502 Packaging Lot No. 900464	500509

Product	Test	Reference
Manufacture Date	01/05/2010	N/A
Expiration Date	N/A	Aug 2012
Strength	200 mg	200 mg
Dosage Form	Soft Gelatin Capsule	Soft Gelatin Capsule
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency (%)	98.5	98.7
Content Uniformity (mean, %CV)	Mean: 99.3 %CV: 0.6%	Mean: 98.3 %CV: 0.7%
Dose Administered	200 mg	200 mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	Group 1: 60 enrolled / 60 dosed all 3 periods / 60 analyzed Group 2: 42 enrolled / 40 dosed all 3 periods / 40 analyzed
No. of Sequences	3
No. of Periods	3
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	**Group 1:** **ABB:** 102, 103, 108, 113, 115, 116, 123, 124, 125, 126, 134, 135, 136, 138, 139, 140, 144, 147, 154, 158 **BBA:** 101, 106, 107, 110, 118, 121, 122, 127, 129, 130, 131, 132, 137, 141, 143, 146, 149, 151, 156, 160 **BAB:** 104, 105, 109, 111, 112, 114, 117, 119, 120, 128, 133, 142, 145, 148, 150, 152, 153, 155, 157, 159 **Group 2:** **ABB:** 201, 203, 204, 205, 208, 220, 225, 226, 228, 233, 236, 237, 240, 241 **BBA:** 202, 206, 207, 215, 216, 218, 221, 222, 223, 224, 231, 234, 235, 239 **BAB:** 209, 210, 211, 212, 213, 214, 217, 219, 227, 229, 230, 232, 238, 242
Blood Sampling Times	**Pre-Dose:** Three (3) blood samples (2 × 6 mL each) were obtained at -1.00, -0.50, and 0.00 hours pre-dose. **Post-Dose:** Sixteen (16) blood samples (1 × 6 mL each) were obtained at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 15.00, 18.00 and 24.00 hours post-dose.

Blood Volume Collected/Sample	During each study period, 19 blood samples were collected from each subject by direct venipuncture or by (b) (4) intravenous catheter using pre-cooled, labeled blood collection tubes containing **K2EDTA** as the anticoagulant. Over the course of the entire study, approximately 413.5 mL of blood was collected from each subject (17.5 mL for pre-study labs, and 396 mL for PK blood samples).
Blood Sample Processing/Storage	The blood samples were stored in an ice bath before centrifugation and were centrifuged within 30 minutes from the moment of blood collection under refrigerated conditions (at 4°C) at 3000 rpm for 10 minutes. The collected plasma from each blood collection tube was aliquotted (in approximately equal volumes) into 2 pre-cooled polypropylene tubes labelled aliquot 1 and aliquot 2. The plasma was aliquotted without pipetting the fuzzy coat that formed at the interface. The samples were immediately flash frozen in an upright position, in a dry ice-acetone bath, and then stored at -20 ± 10°C (or colder) until assayed. The time from blood draw to transferring plasma tubes into the freezer did not exceed 90 minutes
IRB Approval	Approved January 21, 2010
Informed Consent	YES (February 3, 2010)
Length of Fasting Before Meal	Subjects fasted over night and were served the standard FDA meal 30 minutes prior to dosing in all three periods.
Length of Confinement	Subjects were admitted to the Comstock clinic the day before dosing, and remained until the 24.00 hour post-dose blood draw of each period, at which time they were allowed to leave the clinic. Subjects were enrolled in the study as either part of Group 1 or Group 2.
Safety Monitoring	Vital signs (including scheduled blood pressure and pulse rate measurements), diagnostic tests were performed at the times specified in the protocol.
Standard FDA Meal Used?	YES

Comments on Study Design:

- The study design is acceptable (adequate).

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. 3716				
		Treatment Groups		
		Test Product N = 100	Reference Product – First Administration N = 100	Reference Product – Second Administration N = 100
Age (years)	Mean ± SD Range	57.0 ± 5.7 (44 - 70)	57.0 ± 5.7 (44 - 70)	57.0 ± 5.7 (44 - 70)
Age Groups	<18	0 (0%)	0 (0%)	0 (0%)
	18 – 40	0 (0%)	0 (0%)	0 (0%)
	41 – 64	89 (89.0%)	89 (89.0%)	89 (89.0%)
	65 – 75	11 (11.0%)	11 (11.0%)	11 (11.0%)
	> 75	0 (0%)	0 (0%)	0 (0%)
Sex	Male	0 (0%)	0 (0%)	0 (0%)
	Female	100 (100%)	100 (100%)	100 (100%)
Race	Asian/Oriental	11 (11.0%)	11 (11.0%)	11 (11.0%)
	Black	10 (10.0%)	10 (10.0%)	10 (10.0%)
	Caucasian	67 (67.0%)	67 (67.0%)	67 (67.0%)
	Hispanic	11 (11.0%)	11 (11.0%)	11 (11.0%)
	Other	1 (1.0%)	1 (1.0%)	1 (1.0%)
BMI (kg/m^2)	Mean ± SD Range	26.2 ± 3.2 (19.7 - 32.0)	26.2 ± 3.2 (19.7 - 32.0)	26.2 ± 3.2 (19.7 - 32.0)
Other Factors				
Height (cm)	Mean ± SD Range	160.9 ± 6.4 (145 - 176)	160.9 ± 6.4 (145 - 176)	160.9 ± 6.4 (145 - 176)
Weight (kg)	Mean ± SD Range	67.9 ± 9.7 (45 - 94)	67.9 ± 9.7 (45 - 94)	67.9 ± 9.7 (45 - 94)

Table 23. Dropout Information, Fed Bioequivalence Study

Study No. 3716				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
213	Withdrew due to personal reasons	I	No	N/AP
225	Dismissed on 03-13-2010 at 08:17 due to administrative reasons (inability to completely consume the high fat meal). Last dose that the subject received (in Period II) was the reference treatment.	III	No	N/AP

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups			
	Fed Bioequivalence Study Study No. 3716			
	Test	Reference – First Administration	Reference – Second Administration	End-of-Study
Gastrointestinal disorders [GD]				
Abdominal pain upper	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
Diarrhea	3 (8.6%)	0 (0%)	0 (0%)	0 (0%)
Flatulence	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
Nausea	1 (2.9%)	1 (2.9%)	1 (4.8%)	0 (0%)
Toothache	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)
Vomiting	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
General disorders and administrative site conditions [GDASC]				
Asthenia	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
Fatigue	2 (5.7%)	0 (0%)	0 (0%)	0 (0%)
Hot flush	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
Oedema peripheral	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Investigations [INV]				
Blood pressure decreased	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders [MCTD]				
Back pain	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)
Musculoskeletal pain	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)
Pain in extremity	0 (0%)	0 (0%)	1 (4.8%)	0 (0%)
Nervous system disorders [NSD]				
Dizziness	10 (28.6%)	14 (41.2%)	8 (38.1%)	0 (0%)
Headache	3 (8.6%)	4 (11.8%)	0 (0%)	0 (0%)
Somnolence	9 (25.7%)	10 (29.4%)	7 (33.3%)	0 (0%)
Psychiatric disorders [PD]				
Euphoric mood	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Nightmare	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)
Reproductive system and breast disorders [RSBD]				
Breast tenderness	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)
Respiratory, thorasic and mediastinal disorders [RTMD]				
Throat irritation	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders [VD]				
Hypotension	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Presyncope	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)
Total	35 (100%)	34 (100%)	21 (100%)	0 (0%)

Table 25. Protocol Deviations, Fed Bioequivalence Study

Study No. 3716		
Type	Subject #s (Test)	Subject #s (Ref.)
Course of action was not determined for an out of range repeat vital signs.	130, 201, 237	214, 217, 218, 228, 238, 242
Course of action was not followed for an out of range repeat vital signs.	209, 210	N/A

Study No. 3716		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Repeat out of range vital signs was performed outside the required time frame	N/A	218
Health Status Monitoring was not done during clinic exit .	128	N/A
Pulse rate was not recorded at 4.00 time point Period II.	N/A	228
Body Temperature was measured in error during end of study assessment	N/A	225
No Blood sample was obtained due to difficulty experienced during blood collection	154, 158, 146, 210	103, 152, 215
Only 1 collection tube was taken for pre-dose sample.	N/A	152, 203, 204
Centrifugation of samples was outside the required time frame ranging from 1 minute to 28 minutes late during Period I	125, 102, 103, 108,113,115,116, 123, 126, 134-136, 138,-140, 154	101,104-107, 109-112, 114, 117-122, 133, 141, 142 127-132,137, 149-153, 155
Centrifugation of samples was outside the required time frame ranging from 1 minute to 33 minutes late during Period II	104, 105, 109,111, 112, 114, 117, 119, 120, 128, 133, 142, 145, 150, 152, 153, 155 157	101-103, 106-108, 110, 113, 115, 116, 118, 121, 122-124, 125-127, 129-132, 134, 135, 136-141, 143, 144, 156, 149, 151, 154, 158
Centrifugation of samples was outside the required time frame ranging from 1 minute to 30 minutes late during Period III	101, 106, 107,110, 127, 129, 130-132, 137, 141, 143, 146, 149, 151, 156	102-105, 108, 109, 111, 112, 113, 114 125, 126, 128, 133, 134, 135, 136,138-140, 142, 144, 145, 150, 152-155, 157, 158
The following samples were transferred to the freezer late ranging from 1 minute to 26 minutes during Period I	102, 103, 108,113,115,116, 123-126, 138	101,104-107, 109-112, 114, 117-122, 127-132,137
The following samples were transferred to the freezer late ranging from 1 minute to54 minutes during Period II	104, 105, 109,111, 112, 114, 117, 119, 120, 128, 133, 142, 145, 148, 150, 152, 153, 155 157, 159	101-103, 106-108, 110, 113, 115, 116, 118, 121-127, 129-132, 134, 135, 136-141, 143, 144, 146, 147, 149, 151, 154, 156, 158, 160
The following samples were transferred to the freezer late ranging from 1 minute to 38minutes during Period III	101, 106, 107,110, 118, 121, 122, 127, 129, 130, 137, 149, 151	102-105, 108, 109, 111-117,119, 120, 125, 126, 128, 138, 139,150, 152, 153
Centrifugation of samples was outside the required time frame ranging from 1 minute to 12 minutes late during Period I	201,203, 225, 226, 228	202, 213-218, 227, 229, 230
Centrifugation of samples was outside the required time frame ranging from 1 minute to 13minutes late during Period II	214, 217, 219, 227, 229	201-205, 215, 216, 218, 225, 226, 228
Centrifugation of samples was outside the required time frame ranging from 1 minute to 35 minutes late during Period III	202,206, 207, 215, 216, 218, 221-224, 231, 235	201, 203-205, 208-212, 214, 217, 219, 220, 225-230, 232, 233, 236

Study No. 3716		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
The following samples were transferred to the freezer late ranging from 1 minute to 24minutes during Period I	201, 203-205, 208, 220, 225, 226, 228, 237, 240, 241	202, 206, 207, 209-211, 213-219, 221-224, 227, 229-232, 238, 239, 242
Time of Transfer to the freezer cannot be determined due to the discrepancies on the documentation at 6.00 hr time point Period I	225, 226, 228, 233, 236	227, 229-232, 234, 235
The following samples were transferred to the freezer late ranging from 1 minute to 29minutes during Period III	202, 206, 207, 215, 216, 218, 221, 222, 231, 234, 235	201, 203-205, 208-211, 214, 217, 219, 220, 226, 227-230,232, 233, 236-238
The washout period between Period II and Period III was one hour shorter because of the daylight savings time occurred on March 14, 2010	209-214, 217, 219, 227, 229, 230 232, 238, 242, 202, 206, 207, 215, 216, 218,221-224, 231,234, 235, 239	201-208, 215, 216, 218, 220-226 228, 231, 233-237, 239-241 201, 203-205, 208-212,214, , 217,219, 220, 226-230, 232, 233, 236-238, 240-242

Comments on Adverse Events/Protocol Deviations:

- Subject #107 vomited during period III (Test product dosing) on February 28, 2010 at 7:05 PM. Subject #107 was dosed with the test product at 7:42 AM on the same day, nearly 12 hours after dosing. With Tmax occurring at approximately 3.5 hours (2 x 3.5 = 7 hours), this reviewer finds it acceptable to keep subjects #107 in the data analysis.

- The reviewer finds the handling of adverse events/protocol deviations as acceptable (adequate).

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. 3716 (Version 2.0, Amendment 1) Progesterone										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	0.600	3.00	15.0	30.0	60.0	90.0	135	150
Inter day Precision (%CV)	3.0	5.7	4.1	3.3	2.7	2.4	2.1	2.9	3.8	4.7
Inter day Accuracy (%Bias)	-0.1	0.0	-0.7	2.0	2.7	2.3	1.0	-0.2	-3.0	-4.7
Linearity	0.9921 to 0.9999									
Linearity Range (ng/mL)	0.100 to 150									
Sensitivity/LOQ (ng/mL)	0.100									

Bioequivalence Study No. 3716 (Version 2.0, Amendment 1) Progesterone					
Parameter	**Quality Control Samples**				
Concentration (ng/mL)	0.300	0.801	10.0	45.0	110
Inter day Precision (%CV)	6.1	4.4	3.4	2.5	3.2
Inter day Accuracy (%Bias)	-7.0	-0.4	4.0	2.0	-0.9

Comments on Study Assay Validation:

Acceptable (adequate)

Any interfering peaks in chromatograms?	TBD
Were 20% of chromatograms included?	NO
Were chromatograms serially or randomly selected?	N/A

TBD=To Be Determined

Comments on Chromatograms:

With regard to the fed BE study, the firm did not submit the following:

1. "Analyst" spreadsheet with all of the data for both the analyte and the internal standard for the entire study.
2. 20% representative chromatograms
3. Complete Analytical Report (the analytical report submitted did not include the "Summary of Repeats for Analytical Reasons and Reassay for Progesterone in Human Plasma" Table).

Because of these missing items, this reviewer was unable to validate that the reanalysis of subject samples for the fed BE study are acceptable by the DBE.

The firm will be asked to submit the aforementioned missing items for review. The reanalysis data are incomplete (inadequate) at this time.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
DH 8.5	March 16, 2009	Coding of Study Samples, Calibration Standards and Quality Control Samples, Selection of Repeats and Data Reporting

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	See comments on chromatograms above
Did recalculation of PK parameters change the study outcome?	See comments on chromatograms above
Does the reviewer agree with the outcome of the repeat assays?	See comments on chromatograms above
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Incomplete (inadequate)

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 33 and Figure 2

Not Adjusted for Baseline Progesterone Levels:

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT	ng hr/mL	65.902	125.40	74.929	113.87	71.494	143.19	0.88	0.92	1.05
AUCI	ng hr/mL	75.012	119.62	94.863	102.97	84 562	131.76	0.79	0.89	1.12
CMAX	ng/mL	37.743	162.11	43.745	144.66	41 577	215.49	0.86	0.91	1.05
TMAX	hr	3.500	.	3.500	.	4.000	.	1.00	0.88	0.88
KE	hr-1	0.122	30.89	0.118	31.10	0 129	49.44	1.03	0.95	0.92
THALF	hr	6.086	22.98	6.318	24.74	6.061	26.07	0.96	1.00	1.04

* Tmax values are presented as median, range

Baseline Adjusted:

		Test		Reference 1		Reference 2		RatioT/R1	RatioT/R2	RatioR1/R2
Parameter	Unit	Mean	CV%	Mean	CV%	Mean	CV%	(T/R1)	(T/R2)	(R1/R2)
AUCT	ng hr/mL	65.128	127.02	75.964	113.02	69 212	137.30	0.86	0.94	1.10
AUCI	ng hr/mL	74.778	120.06	93.740	103.91	83 578	132.54	0.80	0.89	1.12
CMAX	ng/mL	37.706	162.31	43.737	144.69	41.482	215.63	0.86	0.91	1.05
TMAX	hr	3.500	.	3.500	.	4.000	.	1.00	0.88	0.88
KE	hr-1	0.126	29.97	0.122	32.74	0 132	49.16	1.03	0.96	0.93
THALF	hr	5.870	23.14	6.139	24.62	5 953	26.74	0.96	0.99	1.03

* Tmax values are presented as median, range

The reviewer notes that the baseline adjusted AUCT determination for the reference 1 product (highlighted yellow above) was actually greater than for the unadjusted determination, which was unusual. However, the reviewer did not find any errors in the calculation or data spreadsheet; therefore, the results are assumed to be correct.

Table 30. Geometric Means and 90% Confidence Intervals - Firm Calculated

Progesterone Dose (1 × 200 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study (Study No. 3716) – Baseline Adjusted Data				
Parameter	**Test**	**Reference**	**Ratio of Means**	**90% Confidence Interval**
AUC_{0-t}	42.81	44.96	95.22%	86.45% to 104.88%
AUC_{∞}	49.02	52.54	93.30%	82.84% to 105.09%
C_{max}	18.15	18.68	97.17%	83.46% to 113.14%
Fed Bioequivalence Study (Study No. 3716) – Baseline Non-Adjusted Data				
Parameter	**Test**	**Reference**	**Ratio of Means**	**90% Confidence Interval**
AUC_{0-t}	43.44	45.22	96.06%	87.34% to 105.64%
AUC_{∞}	49.15	53.58	91.73%	81.33% to 103.47%
C_{max}	18.21	18.69	97.43%	83.73% to 113.39%

Table 31. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Not Adjusted for Baseline Progesterone Levels:

Progesterone Capsule 200 mg (1 x 200 mg) Fed BE Study No. 3716, n = 100 (all post-menopausal females) Summary of Statistical Analysis – Unscaled Data Least Square Geometric Means, Point Estimates and 90% Confidence Intervals					
	Geometric Means			**90% CI**	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	43.24	45.00	0.96	87.38	105.71
LCMAX	18.08	18.56	0.97	83.73	113.37

Scaled Data								
Parameter	**T/R Ratio**	**Lower 90% CI**	**Upper 90% CI**	**s2wr**	**sWR**	**Criteria Bound**	**Method Used**	**OUTCOME**
AUC0-t (ng·hr/mL)	0.96	87.38	105.71	0.4376655	0.6615629	-0.27843	Scaled/PE	**PASS**
AUC∞ (ng·hr/mL)	0.89	.	.	0.3979153	0.6308053	-0.209422	Scaled/PE	**PASS**
Cmax (ng/mL)	0.97	83.73	113.37	1.0715266	1.0351457	-0.687524	Scaled/PE	**PASS**

Baseline Adjusted:

Progesterone Capsule
200 mg (1 x 200 mg)
Fed BE Study No. 3716, n = 100 (all post-menopausal females)
Summary of Statistical Analysis – Unscaled Data
Least Square Geometric Means, Point Estimates and 90% Confidence Intervals

	Geometric Means			90% CI	
Parameter	**Test**	**Reference**	**T/R Ratio**	**Lower CI**	**Upper CI**
LAUCT	42.56	44.66	0.95	86.49	104.97
LCMAX	18.01	18.54	0.97	83.47	113.12

Scaled Data

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	Method Used	OUTCOME
AUC0-t (ng·hr/mL)	0.95	86.49	104.97	0.4338851	0.6586996	-0.274693	Scaled/PE	**PASS**
AUC∞ (ng·hr/mL)	0.90	.	.	0.4488096	0.6699325	-0.246303	Scaled/PE	**PASS**
Cmax (ng/mL)	0.97	83.47	113.12	1.0730172	1.0358654	-0.688154	Scaled/PE	**PASS**

Table 32. Additional Study Information

Not Adjusted for Baseline Progesterone Levels:

	Test	Reference 1	Reference 2
Kel and AUC∞ determined for how many subjects?	85	72	64
Do you agree or disagree with firm's decision?	AGREE	AGREE	AGREE
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	N/A**	N/A	N/A
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	Yes	Yes	Yes

** Progesterone is endogenous hormone.

Treatment	n	Mean	Minimum	Maximum
Test	85	0.96	0.90	0.98
Reference 1	72	0.96	0.90	0.99
Reference 2	64	0.96	0.90	0.99

Baseline Adjusted:

	Test	Reference 1	Reference 2
Kel and AUC∞ determined for how many subjects?	85	72	64
Do you agree or disagree with firm's decision?	AGREE	AGREE	AGREE
Indicate the number of subjects with the following:			
measurable drug concentrations at 0 hr	N/A**	N/A	N/A
first measurable drug concentration as Cmax	0	0	0
Were the subjects dosed as more than one group?	Yes	Yes	Yes

Treatment	n	Mean	Minimum	Maximum
Test	85	0.96	0.92	0.99
Reference 1	73	0.96	0.90	1.00
Reference 2	65	0.96	0.90	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer used the SAS code "Continu2" in order to verify the firm's statistical analysis. There was no TRT*GRP effect.

- Statistical analysis was carried out both on baseline adjusted (subtract mean of -1, -.5 and 0 hour predose concentrations) and unadjusted plasma concentrations. However, the reviewer was not able to validate the adjusted plasma concentrations were correct because the firm failed to submit the baseline measurements on a spreadsheet (i.e. -1, -0.5 and 0 hour blood draws). The firm will be asked to submit this data in a SAS transport file.

- The test product meets bioequivalence criteria under fed conditions regardless of whether the unscaled or reference scaled average approach is used (based on reviewer's calculations).

- The median Tmax values from the fed study calculated by the reviewer for progesterone are similar between test and reference products (Test: 3.5 hours; Reference: 3.5 and 4 hours for ref 1 and ref 2 dosing, respectively).

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

The firm's *in vivo* BE study under fed condition is **incomplete (inadequate)** due to the deficiencies listed in Deficiency Comments Section of this review.

Table 33. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Not Adjusted for Baseline Progesterone Levels:

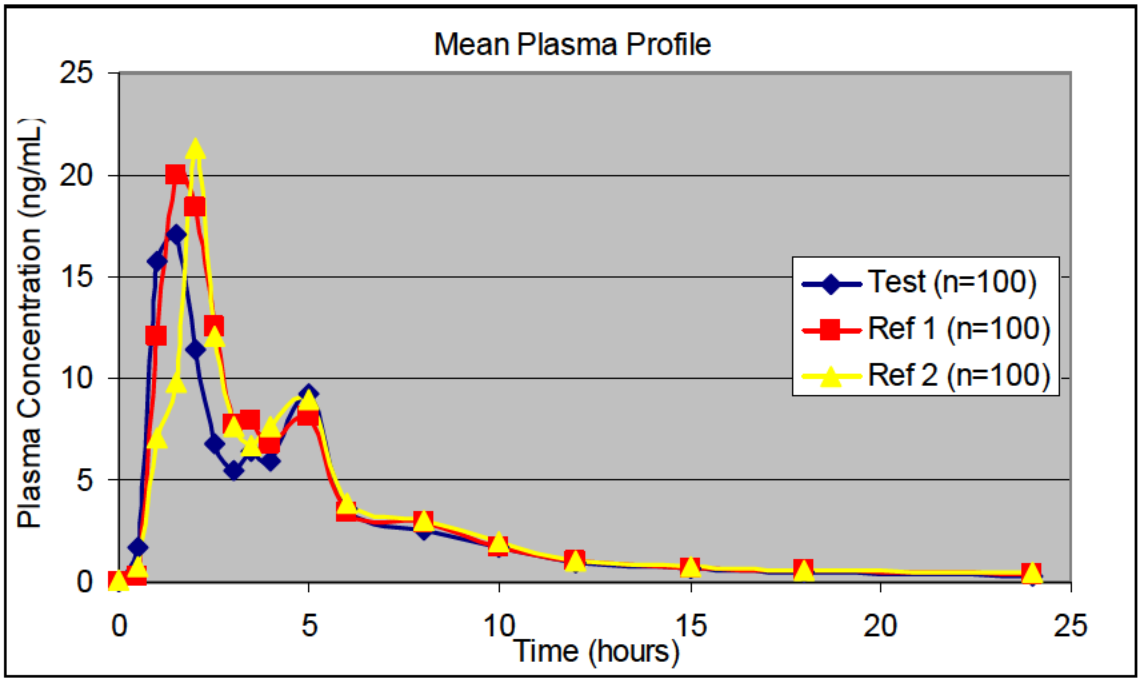
	Test (n=100)		Reference 1 (n=100)		Reference 2 (n=100)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.03	772.54	0.01	378.63	0.09	947.31	3.44	0.40	0.12
0.50	1.72	560.32	0.30	379.42	0.80	564.79	5.82	2.14	0.37
1.00	15.71	356.86	12.09	345.10	7.11	362.31	1.30	2.21	1.70
1.50	17.11	267.94	20.04	234.25	9.81	237.51	0.85	1.74	2.04
2.00	11.42	183.22	18.38	222.24	21.32	412.50	0.62	0.54	0.86
2.50	6.79	154.45	12.51	214.55	12.06	295.71	0.54	0.56	1.04
3.00	5.43	138.31	7.71	179.94	7.61	209.56	0.70	0.71	1.01
3.50	6.43	145.14	7.96	194.01	6.70	209.87	0.81	0.96	1.19
4.00	5.93	133.39	6.82	163.36	7.61	175.58	0.87	0.78	0.90
5.00	9.29	251.53	8.11	138.01	8.92	178.82	1.15	1.04	0.91
6.00	3.62	189.52	3.44	95.24	3.88	115.60	1.05	0.93	0.89
8.00	2.53	121.60	2.92	180.57	3.01	141.13	0.87	0.84	0.97
10.00	1.72	133.68	1.73	117.54	1.97	118.03	1.00	0.87	0.88
12.00	0.90	98.60	1.03	113.84	1.06	123.98	0.88	0.85	0.97
15.00	0.63	110.05	0.70	119.17	0.73	159.29	0.90	0.87	0.96
18.00	0.46	107.25	0.55	114.37	0.58	186.09	0.84	0.79	0.94
24.00	0.31	102.07	0.36	106.79	0.45	290.23	0.84	0.68	0.81

Baseline Adjusted:

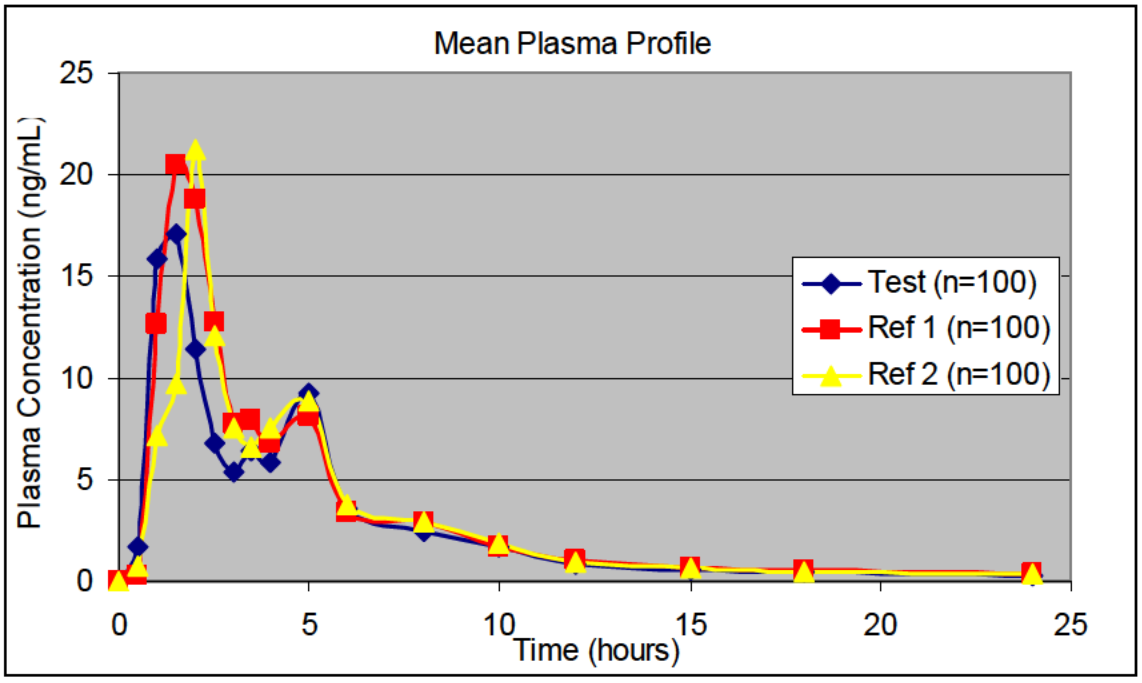
	Test (n=100)		Reference 1 (n=100)		Reference 2 (n=100)		RatioTR1	RatioTR2	RatioR1R2
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R1)	(T/R2)	(R1/R2)
0.00	0.00	.	0.00	.	0.00	.	.	.	.
0.50	1.73	561.91	0.30	376.65	0.73	546.28	5.70	2.38	0.42
1.00	15.86	355.42	12.62	337.27	7.16	353.92	1.26	2.22	1.76
1.50	17.08	268.45	20.46	231.46	9.71	235.32	0.83	1.76	2.11
2.00	11.39	183.88	18.77	219.54	21.23	414.15	0.61	0.54	0.88
2.50	6.76	155.35	12.76	212.00	12.09	295.67	0.53	0.56	1.06
3.00	5.39	139.50	7.70	180.13	7.52	210.39	0.70	0.72	1.02
3.50	6.39	146.21	7.95	194.24	6.60	211.40	0.80	0.97	1.20
4.00	5.89	134.44	6.81	163.59	7.51	176.91	0.87	0.78	0.91
5.00	9.26	252.48	8.10	138.15	8.83	180.56	1.14	1.05	0.92
6.00	3.58	191.59	3.43	95.52	3.78	115.51	1.04	0.95	0.91
8.00	2.49	120.47	2.91	181.09	2.92	142.56	0.86	0.85	1.00
10.00	1.68	132.76	1.72	118.07	1.88	112.05	0.98	0.90	0.92
12.00	0.86	99.86	1.02	115.00	0.97	96.11	0.85	0.89	1.05
15.00	0.60	110.45	0.69	120.92	0.63	98.38	0.86	0.95	1.10
18.00	0.43	106.60	0.54	116.62	0.49	105.73	0.80	0.89	1.11
24.00	0.28	92.59	0.36	109.90	0.34	123.88	0.78	0.80	1.03

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

Not Adjusted for Baseline Progesterone Levels:



Baseline Adjusted:



4.2 Formulation Data

Ingredient	Pharmaceutical Function	Amount (mg) / Capsule		Amount (%) / Capsule	
		100 mg	200 mg	100 mg	200 mg
(b) (4)					
Progesterone, USP (Micronized)		100.00	200.00	40.00	40.00
Lecithin, NF					(b) (4)
Peanut Oil, NF					
Total					
(b) (4)					
Gelatin, NF (b) (4)					(b) (4)
Glycerin USP (b) (4)					
Iron Oxide Red	(b) (4)	(b) (4)	N/A	(b) (4)	--
Yellow Iron Oxide		N/A	(b) (4)	--	(b) (4)
Titanium Dioxide, USP					(b) (4)
(b) (4)					
Total					
Printing ink:					
Ink, Black (b) (4)			(b) (4)	--	--
(b) (4)				--	--
				--	--

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(b) (4)

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	YES
If no, are they all above/within IIG (per day) limits?	Within IIG Limits
If no, are additional data or Pharm/Tox consult necessary?	N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	YES
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	YES
Are all strengths of the RLD product dose-proportional?	YES
Are all strengths of the test formulation acceptable	**ACCEPTABLE (ADEQUATE)**
Additional Attachment for Formulation Calculations	N/A

4.3 Dissolution Data

Dissolution Review Path	DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive

Table 34. Dissolution Data

OLD UNACCEPTABLE DATA (reviewed previously):
100 mg strength:

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Baskets, 20 Mesh)
	Speed of Rotation:	100 rpm
	Medium:	5% SDS in 0.1 HCl
	Volume:	1000 mL
	Temperature:	37.0 ± 0.5˚C
Firm's Proposed Specifications	Meets current USP <905> acceptance value and range (as specified) L=1 15.0 and 25.0	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. (Subsidiary of Teva Pharmaceuticals USA) 223 Quaker Road Pomona, NY 10970	

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 2 hours	4 hours	6 hours	8 hours	10 hours	Study Report Location
Study Report #: ARD-RPT-4538	03/01/2010 03/02/2010	Test Product Name: Progesterone Capsules, 100 mg Batch No.: 0001019501 Manufacturing Date: 01/05/2010	100 mg Capsules	12	Mean	43	83	96	97	97	Module 5.3.1.3
					Range	(b) (4)					
					%CV	5.5	8.1	2.6	1.4	1.5	
Study Report #: ARD-RPT-4538	03/01/2010 03/02/2010	Reference Product Name: PROMETRIUM® (progesterone, USP) Capsules, 100 mg Lot No.: 500309 Expiration Date: September 2011	100 mg Capsules	12	Mean	46	81	92	95	96	
					Range	(b) (4)					
					%CV	8.4	12.6	9.8	5.3	3.0	

200 mg strength:

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Baskets, 20 Mesh)
	Speed of Rotation:	100 rpm
	Medium:	5% SDS in 0.1 HCl
	Volume:	1000 mL
	Temperature:	37.0 ± 0.5˚C
Firm's Proposed Specifications	Meets current USP <905> acceptance value and range (as specified) L=1 15.0 and 25.0	
Dissolution Testing Site (Name, Address)	Barr Laboratories, Inc. (Subsidiary of Teva Pharmaceuticals USA) 223 Quaker Road Pomona, NY 10970	

Study Ref No.	Testing Dates	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours) 2 hours	4 hours	6 hours	8 hours	10 hours	Study Report Location
Study Report #: ARD-RPT-4528	02/03/2010 02/04/2010	Test Product Name: Progesterone Capsules, 200 mg Batch No.: 0001019502 Manufacturing Date: 01/05/2010	200 mg Capsules	12	Mean	28	58	83	93	95	Module 5.3.1.3
					Range	(b) (4)					
					%CV	9.8	11.8	11.4	4.7	2.1	
Study Report #: ARD-RPT-4528	02/03/2010 02/04/2010	Reference Product Name: PROMETRIUM® (progesterone, USP) Capsules, 200 mg Lot No.: 500509 Expiration Date: August 2012	200 mg Capsules	12	Mean	28	71	94	96	97	
					Range	(b) (4)					
					%CV	7.1	15.5	9.2	4.4	1.2	

NEW DATA (reviewed here):

Progesterone Capsules, 100 mg Batch Number 0001019501 Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)						
Capsule #	% Dissolved					
	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	32	91	96	100	101	101
Max	(b) (4)					
Min						
% RSD	24.8	11.9	7.1	1.4	1.6	1.5
Reference	PR9905/58-59					
Date of Testing	01/11/2011					

Prometrium® (progesterone, USP) Capsules 100 mg LOT: 500309 EXP: SEPT 2011; Manufactured by Solvay Pharmaceuticals						
Capsule #	% Dissolved					
	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	22	83	102	102	103	104
Max	(b) (4)					
Min						
% RSD	20.9	13.1	1.2	1.2	1.6	1.3
Reference	PR9905/58-59					
Date of Testing	01/11/2011					

Comparative Dissolution Profiles Study

Progesterone Capsules, 100 mg

Batch Number: 0001019501

Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)

VS

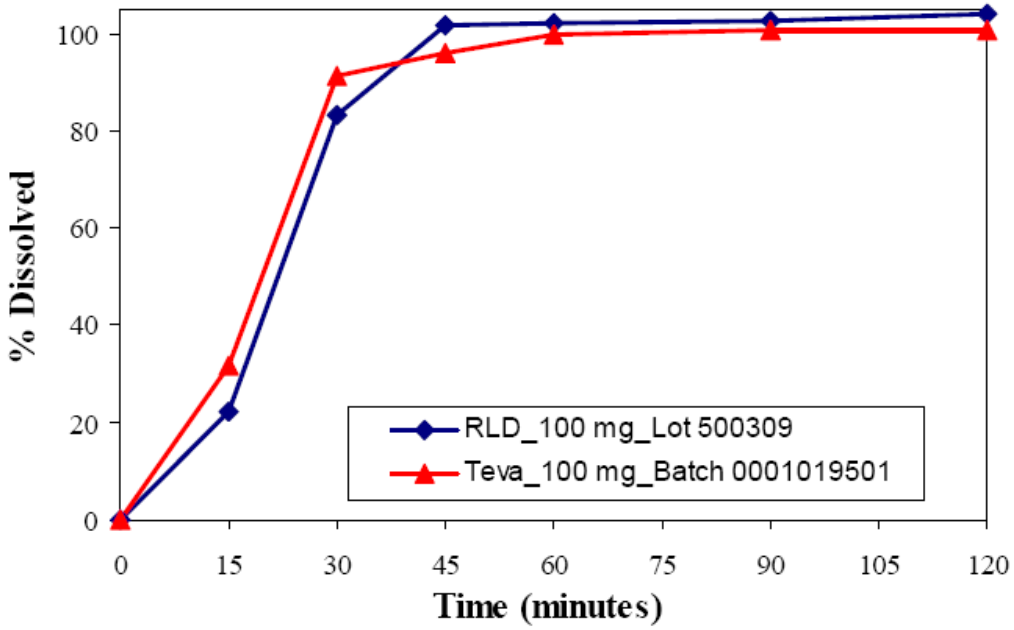
Prometrium® (progesterone, USP) Capsules 100 mg

LOT: 500309 EXP: SEPT 2011

Manufactured by SOLVAY PHARMACEUTICALS

(Average of 12 Capsules)

Figure 1



Progesterone Capsules, 200 mg Batch Number 0001019502 Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)						
Capsule #	% Dissolved					
	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	32	91	100	101	102	101
Max	(b) (4)					
Min						
% RSD	23.3	8.8	1.3	2.0	2.1	1.6
Reference	PR9905/77-78					
Date of Testing	01/10/2011					

Prometrium® (progesterone, USP) Capsules 200 mg LOT: 500509 EXP: AUG 2012; Manufactured by Solvay Pharmaceuticals						
Capsule #	% Dissolved					
	15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	24	74	96	98	99	100
Max	(b) (4)					
Min						
% RSD	5.2	19.4	3.6	1.2	1.0	1.0
Reference	PR9905/77-78					
Date of Testing	01/10/2011					

Comparative Dissolution Profiles Study

Progesterone Capsules, 200 mg

Batch Number: 0001019502

Manufactured by Catalent Pharma Solutions for Teva (Barr Laboratories, Inc.)

VS

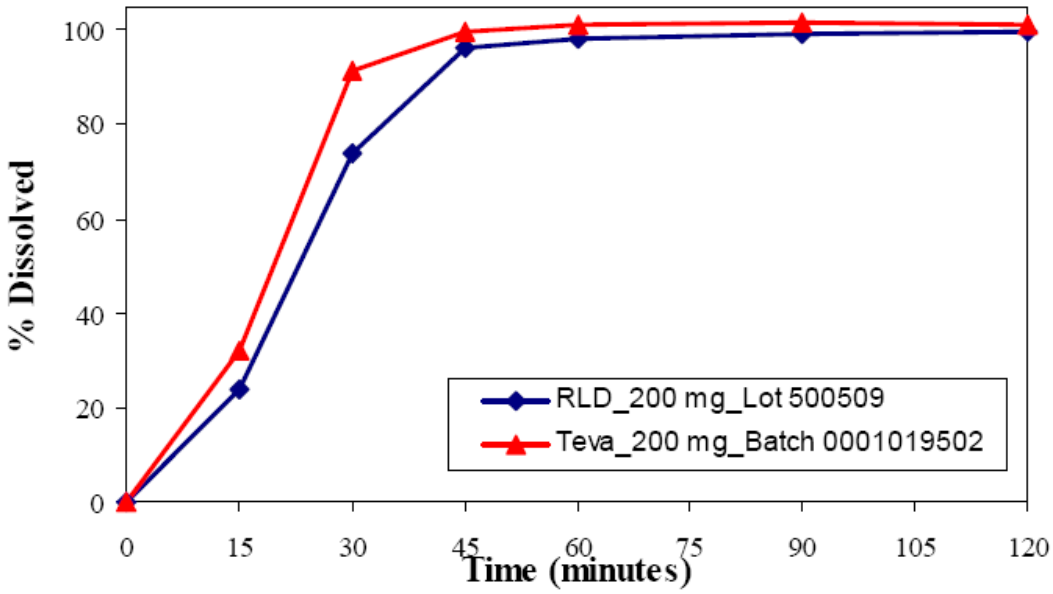
Prometrium® (progesterone, USP) Capsules 200 mg

LOT: 500509 EXP: AUG 2012

Manufactured by SOLVAY PHARMACEUTICALS

(Average of 12 Capsules)

Figure 1



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BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 202121

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Progesterone Capsule, 100 mg and 200 mg

The Division of Bioequivalence (DBE) has completed its review and the following deficiencies have been identified:

1. The average recovery of internal standard (IS) (%) for the validated bioanalytical method used in the fasting bioequivalence (BE) study was greater than 100% (111.2%). Please explain this result (i.e. possible reason for greater than 100%) and discuss any impact on the results of the fasting bioequivalence (BE) study.

2. Please submit the chromatograms for all subject samples from the fasting and fed BE studies flagged as unacceptable chromatography (UC). In addition, please submit additional 20% representative chromatograms for the fed study, starting with the first subject.

3. For the fed BE study, you did not submit any raw numerical data from the assay runs for any of the subjects (i.e. analyst spreadsheets). Please submit complete raw numerical data of all assay and reassay runs, including the data of peak area/height for the drug, peak area/height for the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples.

4. In addition, for the fed study, please submit a complete bioanalytical study report, including within study assay validation results, reassay tables comparing the original values with the reassayed values, etc. This report should be similar to that submitted for the fasting study.

5. Lastly, please submit the -1, -0.5 and 0 hour (baseline) data for each subject from each study period of the fed BE study in a SAS transport file (.XPT).

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 202121

Reviewer: DeHaven, Wayne **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Progesterone Capsule, 100 mg and 200 mg

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal
14389	6/11/2010	Bioequivalence Study	Fasting Study	1	1
14389	6/11/2010	Bioequivalence Study	Fed Study	1	1
14389	6/11/2010	Other	Dissolution Waiver	1	1
14389	3/3/2011	Other	Dissolution Amendment	1	1
				Bean Total:	4

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

/s/

WAYNE I DEHAVEN
07/26/2011

SHRINIWAS G NERURKAR
07/26/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
07/28/2011

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	202121		
Drug Product Name	Progesterone Capsule		
Strength(s)	100 mg and 200 mg		
Applicant Name	Teva Pharmaceuticals, USA		
Address	400 Chestnut Ridge Road Woodcliff Lake, NJ 07677		
Applicant's Point of Contact	Robert S. Vincent, Director – Regulatory Affairs		
Contact's Telephone Number	(201) 930-3610 or (210) 930-2233		
Contact's Fax Number	(201) 489-1403		
Original Submission Date(s)	June 11, 2010 March 3, 2011 (new dissolution data submitted)		
Submission Date of Amendment Under Review	August 26, 2011		
Reviewer	Wayne DeHaven, Ph.D.		
Study Number (s)	11036003	3716	
Study Type (s)	Fasting	Fed	
Strength (s)	200 mg	200 mg	
Clinical Site	Novum Pharmaceutical Research Services	Biovail Contract Research (a Division of Biovail Corporation)	
Clinical Site Address	3760 Pecos McLeod Las Vegas, NV 89121 702-435-3739	460 Comstock Road / 689 Warden Ave. Unit 1 Toronto, Ontario, Canada M1L 4S4 / M1L 4R6	
Analytical Site	(b) (4)		
Analytical Address			
OUTCOME DECISION	**ADEQUATE**		
Waiver Request Result	**ADEQUATE**		
DSI Report Result	**ADEQUATE**		
BE Study Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
1, 6	Dissolution	(b) (4) 100 mg, 200 mg and (b) (4)	**ADEQUATE**
1, 9	Fasting Study	(b) (4)	**ADEQUATE**
1, 9	Fed Study		**ADEQUATE**

Review of an Amendment

1 EXECUTIVE SUMMARY

This is a review of an amendment submitted by Teva Pharmaceuticals regarding ANDA #202121, Progesterone Capsules, 100 mg and 200 mg. The reference listed drug (RLD) for this application is Abbott's Prometrium® (Progesterone) Capsule, which is indicated for use in the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women receiving conjugated estrogens tablets. Prometrium® is also indicated for use in secondary amenorrhea

This amendment was submitted in response to a deficiency letter faxed to Teva on August 1, 2011. In the deficiency letter, Teva was asked the following:

1. Explain possible reason for greater than 100% recovery for the internal standard (IS), and discuss any possible impact on the results of the fasting BE study;
2. Submit all chromatograms flagged as "unacceptable chromatography" (UC), as well as additional 20% representative chromatograms for the fed BE study;
3. Submit all of the raw numerical data from the assay runs for the fed BE study;
4. Submit a complete bioanalytical report for the fed BE study; and
5. Submit the baseline data for each subject from the fed BE study.

Teva responded adequately to the five deficiencies listed above (see Section 4C – Review of Submission below).

No Office of Scientific Investigations (OSI) inspections are pending or necessary (see Section 5 – Review of OSI Findings).

The DBE accepts the waiver of *in vivo* bioequivalence study requirements for the 100 mg strength capsule under the Section 21 CFR § 320.22 (d) (2).

The FDA acknowledges that Teva will continue to use the following dissolution method and specification:

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Specification:	NLT (b) (4) (Q) dissolved in 45 minutes

*To avoid excess foam formation, two drops of simethicone should be added.

The application is **acceptable (adequate).**

2 TABLE OF CONTENTS

3 BACKGROUND

The following table summarizes the DBE history regarding this ANDA:

DBE Review	Location of review in DARRTS	Submission Date of Supporting Document	Supporting Document #	Deficiencies
"Dissolution only" review	DEHAVEN, WAYNE I 12/01/2010 N/A 12/01/2010 REV-BIOEQ-02(Dissolution Review) Original-1 (Unknown) Archive	08/17/2010	1	The DBE recommended the firm develop a more appropriate dissolution method for the test product
"Full ANDA" review	DEHAVEN, WAYNE I 07/28/2011 N/A 07/28/2011 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive	08/17/2010 and 03/03/2011	1, 6 (dissolution amendment)	This amendment was submitted in response to a deficiency letter dated August 1, 2011. In the deficiency letter, Teva was asked the following: 1. Explain possible reason for greater than 100% recovery for the internal standard (IS), and discuss any possible impact on the results of the fasting BE study; 2. Submit all chromatograms flagged as "unacceptable chromatography" (UC), as well as additional 20% representative chromatograms for the fed BE study; 3. Submit all of the raw numerical data from the assay runs for the fed BE study; 4. Submit a complete bioanalytical report for the fed BE study; and 5. Submit the baseline data for each subject from the fed BE study in a SAS transport file.
Amendment #1 review**	Under review here	08/26/2011	9	--

**This review also includes a review of all OSI findings for the 2 clinical and 1 analytical sites.

4 SUBMISSION SUMMARY

A. Drug Product Information, PK/PD Information, and Relevant DBE History

Please see in DARRTS for ANDA # 202121 DEHAVEN, WAYNE I 07/28/2011 N/A 07/28/2011 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	1
Waiver requests	No	--
BCS Waivers	No	--
Failed Studies	No	--
Study Amendment	Yes	1

C. Review of Submission

Deficiency No. 1: The average recovery of internal standard (IS) (%) for the validated bioanalytical method used in the fasting bioequivalence (BE) study was greater than 100% (111.2%). Please explain this result (i.e. possible reason for greater than 100%) and discuss any impact on the results of the fasting bioequivalence (BE) study.

***Firm's Response* (New Data):** According to [redacted] (b) (4): *The calculations and procedure used to determine the recovery of progesterone were verified and confirm that recovery as evaluated in VAL254 is indeed 111.2%. As variability of bioanalytical assays, up to 15% is acceptable, there was no reason to reassess the manner in which the recovery was originally established.*

However, in response to your observation, the procedure for the recovery assessment was investigated.

Briefly, analyte and IS were [redacted] (b) (4) *The comparison of these two sets of samples resulted in a recovery of 97.6%, shown in Attachment I.*

Following this page, 1 page withheld in full (b)(4)

To scientifically test this hypothesis, [redacted] conducted a new recovery study, this time with the [redacted] step for the portion of the study representing 100% recovery carried out in plasma. In this case, the recovery was 97.6%, less than 100%. Therefore, [redacted] hypothesis was correct that the high % recovery for the IS originally reported was due to the less effectiveness of the [redacted] step in [redacted] when compared to plasma.

[redacted] scientifically answered deficiency #1 with new data. The DBE agrees with their conclusion that the high value obtained in the initial IS recovery assessment will not impact on the concentration data of the incurred samples. The response is **acceptable (adequate)**.

Deficiency No. 2: Please submit the chromatograms for all subject samples from the fasting and fed BE studies flagged as unacceptable chromatography (UC). In addition, please submit additional 20% representative chromatograms for the fed study, starting with the first subject.

Firm's response* (No New Data)*: *The chromatograms for all samples originally flagged as unacceptable chromatography are presented in attachment 2 (for the fasted study) and in attachment 3 (for the fed study).*

These samples were flagged UC according to [redacted] *SOP GP 15.6 – Baseline Integration Method (refer to attachment 4).*

One sample was flagged UC as the analyte and the internal standard retention times were outside the acceptable retention time range outlined in the bioanalytical method SOP, as detailed in section 7.3 of SOP 15.6. All remaining samples were flagged UC due to the presence of a positive spike, as detailed in section 7.9 of the SOP.

Reviewer's comments: All of the requested chromatograms were submitted to the Agency. The following is representative of the type of chromatograms which were flagged as UC:

(b) (4)

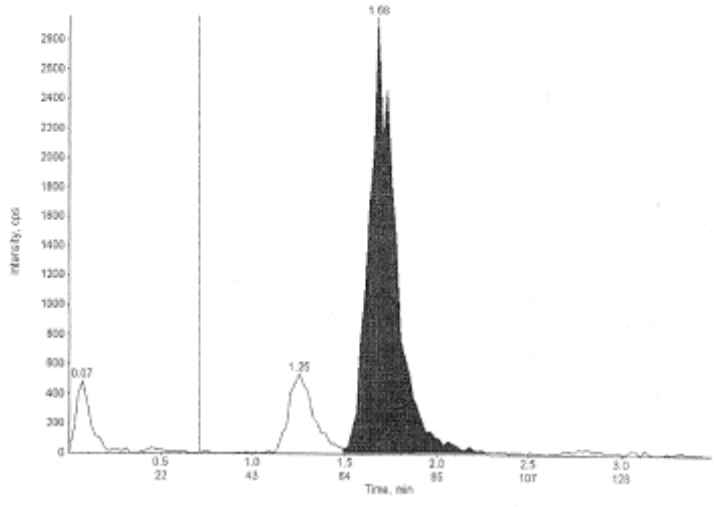
[redacted]

These chromatograms meet the objective criteria established in SOP GP 15.6, specifically the following:

7.9. Spiked or Fissured Peaks

If the peak of interest has an area ratio equal to or greater than the LLOQ standard and a positive spike (Figure 9) or negative fissure (Figure 10) occurs above 50% of the peak height that represents an area difference of greater or equal to 5.0% of the total area, then the mass trace is coded UC – Unacceptable Chromatography. If this criterion is not applied, this should be documented, and justification for not applying the criterion must be provided.

Figure 9: Example of a Spiked Peak



Per the response from (b) (4), there was one sample which was flagged UC as the analyte and IS retention times were outside the acceptable RT range outlined in the bioanalytical method SOP, section 7.3.

In addition, the 20% representative chromatograms for the fed BE study were also submitted, in serial order starting with subject #101.

Based on the submitted chromatograms, there are no concerns regarding the reanalyses of subject samples flagged as UC. The firm's response to deficiency #2 is **acceptable (adequate)**.

Deficiency No. 3: For the fed BE study, you did not submit any raw numerical data from the assay runs for any of the subjects (i.e. analyst spreadsheets). Please submit complete raw numerical data of all assay and reassay runs, including the data of peak area/height for the drug, peak area/height for the internal standard, ratio of the peak area/height for the drug to the peak area/height for the internal standard, dilution factor (if any), and the corresponding concentration for each assayed and reassayed sample of all subject samples, calibration standard concentration samples, and quality control samples.

Firm's response* (No new Data)*: *The raw numerical data from all assay and reassay runs is included in the amended analytical report in Appendix VI of Determination of Progesterone in Human Plasma by LC/MS/MS" (Study Number: P09194_CJK, Clinical Protocol No. 3716, Version 2.0, Amendment 1) located in Module 5.1.3.4.*

Reviewer's comments: The raw numerical data were reviewed and were found complete. Teva's response to deficiency #3 is **acceptable (adequate)**.

Deficiency No. 4: In addition, for the fed study, please submit a complete bioanalytical study report, including within study assay validation results, reassay tables comparing the original values with the reassayed values, etc. This report should be similar to that submitted for the fasting study.

Firm's response* (No New Data)*: *The complete Bioanalytical study report is provided in Module 5.1.3.4 for the Determination of Progesterone in Human Plasma by LC/MS/MS" (Study Number: P09194_CJK, Clinical Protocol No. 3716, Version 2.0, Amendment 1).*

Reviewer's comments: The bioanalytical study report was reviewed and was found **acceptable (adequate)**. The firm's SOPs were correctly followed, and the reviewer agrees with the outcome of the repeat assays.

Deficiency No. 5: Lastly, please submit the -1, -0.5 and 0 hour (baseline) data for each subject from each study period of the fed BE study in a SAS transport file (.XPT).

***Firm's response* (No New Data):** *The requested uncorrected data for BE fed study 3716 can be found in the SAS Files provided in Module 5.*

Reviewer's comments: Statistical analysis was previously carried out on both baseline adjusted and unadjusted plasma concentrations [see in DARRTS for ANDA #202121 DEHAVEN, WAYNE I 07/28/2011 N/A 07/28/2011 REV-BIOEQ-01(General Review) Original-1 (Unknown) Archive]. However, the reviewer was not able to validate the adjusted plasma concentrations were correct because the firm failed to submit the baseline measurements on a spreadsheet (i.e. -1, -0.5 and 0 hour blood draws). In this amendment, Teva has correctly submitted the baseline blood concentrations. The baseline data analyzed in the original review are correct. The test product meets bioequivalence under fed conditions with and without baseline adjustments.

Teva's response to deficiency #5 is **acceptable (adequate)**.

D. Deficiency Comments

None

E. Recommendations

1. The Division of Bioequivalence (DBE) finds the fasting bioequivalence study #11036003 conducted by Teva Pharmaceuticals on its Progesterone Capsule, 200 mg (Lot # 0001019502) comparing it to the reference product, Abbott's Prometrium® (Progesterone, USP) 200 mg Capsules (Lot # 500509), **acceptable (adequate)**.

2. The Division of Bioequivalence (DBE) finds the fed bioequivalence study #3716 conducted by Teva Pharmaceuticals on its Progesterone Capsule, 200 mg (Lot # 0001019502) comparing it to the reference product, Abbott's Prometrium® (Progesterone, USP) 200 mg Capsules (Lot # 500509), **acceptable (adequate)**.

3. The firm's dissolution testing on its Progesterone Capsule, 200 mg (Lot #0001019502, and 100 mg (Lot #0001019501) compared to the reference product, Abbott.'s Prometrium® (Progesterone, USP) 200 mg Capsules (Lot #500509) and 100 mg (Lot #500309) is **acceptable (adequate)**. The DBE acknowledges that the firm will conduct the dissolution testing using the following dissolution method and specification:

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Sampling times:	15, 30, 45 and 60 minutes or till 80% is dissolved.

*To avoid excess foam formation, two drops of simethicone should be added.

Specification: NLT (b) (4) (Q) dissolved in 45 minutes

4. The request for a waiver of the *in vivo* bioequivalence testing requirement for the 100 mg Test products under 21 CFR 320.22(d)(2) is granted.

F. Comments for Other OGD Disciplines

Discipline	Comment
--	None

5 REVIEW OF OSI FINDINGS

1. Clinical Site #1 (Fasted): Novum Pharmaceutical Research Services

This is a review of the OSI Inspection Report for the inspection of the clinical site, Novum Pharmaceutical research Services [DARRTS ANDA (b) (4) FRM-ADMIN-01(Memorandum to File), 08/01/2011]. The inspection was in regards to ANDA # (b) (4) and the inspection was conducted between (b) (4). At the completion of the inspection, a FORM FDA-483 was issued which included the investigator's findings. The findings have previously been reviewed by the DBE [DARRTS ANDA (b) (4) WAHBA, ZAKARIA Z 08/17/2011 N/A 08/17/2011 REV-BIOEQ-01(General Review) Original-1 (Not Applicable) Archive], but without discussion of the impact of these findings on related ANDAs. Therefore, the impact of these findings on ANDA #202121 is reviewed below.

1. For both studies for all patients, there is no documentation that the clocks used to document the time of drug administration are synchronized to the clocks used to document the time of blood sampling.

OSI Response to Observation #1: *Dr. Brimhall, Novum's Medical Director explained at the close of inspection that all clinical areas have large clocks on the walls that are connected to a single server. Novum stated that all time clocks are to be synchronized to the time clock used for dosing in their Standard Operating Procedure (SOP) 2839. Novum also added that they already revised their SOP to record verification of synchronization.*

Reviewer's Comments: The OSI inspection was completed from (b) (4) (b) (4) In ANDA #202121, the clinical portion of the study at Novum was conducted from February to March 2010, before the OSI inspection was completed. Therefore, Novum was not aware of this observation prior to conducting the relevant study under review here. Yet, at the end of the inspection, Novum clarified that all of the clocks were already synchronized and connected to a single server.

If there was difference between the dosing clock and sampling clock at the time of the study, such error would have been carried consistently through all samples. So its impact on the BE outcome is not expected to be significant. From a bioequivalence standpoint, the firm's response is **acceptable (adequate)**.

The following items are reviewed together:

2. The medical records for Subject 212 (Protocol 10914204, Period I) indicate that the blood sample was obtained at 48 hours '+1 minute' due to a 'difficult draw.' The corresponding case report form (CRF) indicates all samples were collected at the scheduled time.

3. The medical records for Subject 319 (Protocol 10914204, Period II) indicate the 60-hr blood sample due at 19:48 was obtained at 19:47. The corresponding case report form (CRF) indicates the sample was collected at the scheduled time.

4. The SOPs require the reason for blood draw deviations to be documented on the back of the draw card. The card for Subject 247 at Period II, 4-hr post dose states 'no sample drawn.' The corresponding CRF indicates that the subject was a 'no show.' Protocol 10914204 indicates the subjects 'will remain in the unit until 24-hr blood sample is collected.'

OSI Responses to Observations #2 - #4: *Novum Pharmaceutical Research responded in writing that they would conduct an intensive training with all applicable staff in order to ensure proper procedure and, accurate transcription of data.*

Regarding observation #2, because the subject was dropped from the study at Period II check-in, the blood samples were not sent for analysis so that the deviation had no impact on the study data.

Regarding observation #3, because the deviation was only one minute, Novum insisted it would have no significant impact on the determination of pharmacokinetic (PK) parameters for the subject. The investigator recommends DB II use the actual blood sampling time for the PK analysis of the Subject.

Regarding observation #4, the subject remained in the facility for 24 hours post dose. The subject's blood draw cards and release log verify the subject's presence.

Reviewer's Comments: The OSI uncovered discrepancies in the sampling times for some of the subjects. However, these discrepancies were very minor (e.g. +1 minute deviations in sampling time) and should not change the outcome of the BE study. This reviewer does not feel that the firm was intentionally trying to hide these time deviations from the Agency. Novum's response to the form FDA-483 observations is acceptable (adequate).

It should be pointed out that the firm used the actual times in their statistical analysis of the BE study. According to the study report for ANDA #202121, "*The scheduled times were used in the pharmacokinetic calculations. In cases where there were blood draw time deviations, the actual times of collection were used.*" In contrast, the reviewer used nominal times. In both cases, the BE study met BE criteria (i.e. sampling time deviations did not change the overall outcome).

As reference, the reported sampling time deviations for ANDA #202121 are included in the following table:

PROGESTERONE
PROTOCOL /STUDY NO. 11036003

Deviations from Scheduled Collection Times* (Page 1 of 2)

Sub. No.	Period	Sample Time (hour)	Deviation [1,2]
01	II	2.0	+4
01	II	3.5	+1
01	III	1.0	+3
01	III	6.0	+4
01	III	8.0	+4
02	I	10.0	+1
02	II	0.5	+2
03	III	18.0	+1
05	I	12.0	+1
06	III	1.0	+1
07	I	10.0	+1
07	III	2.0	+1
07	III	3.0	+2
09	III	0.0	-1
10	I	0.0	-1
12	II	0.0	NS
12	II	5.0	+1
13	I	-0.5	+1
13	II	18.0	+1
15	I	-1.0	+1
15	I	3.5	+4
15	I	5.0	+3
15	I	6.0	+4
15	I	10.0	+1
15	III	-1.0	+2
15	III	10.0	+1
17	I	-1.0	+1
17	I	2.0	+1

[1] Minutes sample was collected late (+) or early (-).
[2] See Case Report Form, *Dose Administration and Blood Collections*, fo reason blood draw time was not on schedule.
* Subjects who did not complete at least two periods of the study (1 test, reference) are not listed.
NS = No Sample

Deviations from Scheduled Collection Times* (Page 2 of 2)

Sub. No.	Period	Sample Time (hour)	Deviation [1,2]
20	III	24.0	+1
21	I	-0.5	+1
21	I	4.0	+2
21	I	5.0	-1
21	I	6.0	+1
21	I	10.0	+1
23	I	2.0	+1
27	I	10.0	+1
32	I	5.0	+2
32	III	-0.5	+4
33	I	2.5	+1
33	I	6.0	+1
33	I	10.0	+4
33	II	12.0	+2
35	I	5.0	+1
36	II	0.5	+2
36	II	12.0	+1
40	I	-0.5	+3
40	I	1.5	+1
40	I	10.0	+1
40	III	10.0	+2

[1] Minutes sample was collected late (+) or early (-).
[2] See Case Report Form, *Dose Administration and Blood Collections*, for reason blood draw time was not on schedule.
* Subjects who did not complete at least two periods of the study (1 test, 1 reference) are not listed.
NS = No Sample

5. According to the blood sampling documentation (Protocol 10914204, Period II), Subject 247 had 'no sample drawn' at 4-hr post dose.

OSI Response to Observation #5: *Novum responded in writing that this deviation was reported in the final study report. Novum confirmed with the sponsor,* (b) (4) (b) (4) *that no concentration estimate was provided for this sample. The investigator recommends DB II confirm this during review of the study report.*

Reviewer's Comments: Observation #5 is not applicable to ANDA #202121.

6. Because of 'staffing issues', 60-hr post-dose samples were drawn late for 16 subjects (Protocol 10914205, Period I) as follows: Subject 301: +18 min, Subject 302: +17 min, Subject 304: +17 min, Subject 305: +16 min, Subject 306: +16 min, Subject 309: +14 min, Subject 310: +14 min, Subject 311: +14 min, Subject 312: +13 min, Subject 314: +12 min, Subject 317: +13 min, Subject 319: +9 min, Subject 320: +9 min, Subject 321: +10 min, Subject 323: +8 min, Subject 324: +8 min

OSI Response to Observation #6: *Novum responded in writing that this observation was an isolated event. All the deviations were reported in the subjects' CRFs and the final study report, and provided to the statistician prior to statistical analysis. The investigator recommends DB II confirm that actual blood sampling times were used for all PK analyses for those subjects listed above during review of the study report.*

Reviewer's Comments: This observation is specific for ANDA (b) (4) and should not impact ANDA #202121.

7. According to the medical record and CRF for Subject 311 (Protocol 10914205, Period I), none of the blood samples were obtained at the proper time. All except 48-hr and 60-hr samples were obtained one minute early because the dose was given one minute later than scheduled time. The times on the pre-printed blood draw cards had not been corrected. (Note: There is a typographical error in investigator's report, subject 311 was typed as subject 331, the correct is subject 311).

OSI Response to Observation #7: *Novum responded in writing that they have changed their process to ensure the availability of a 'backup' doser. Novum insisted that, because Subject 311 did not complete the study, the samples were not sent for drug concentration analysis and the deviation had no impact on the study data. DB II reviewer should verify if Subject 331 was indeed an early drop-out of the study.*

Reviewer's Comments: Subject 311 was drop-out; therefore, no blood samples were obtained for analytical assay. The firm's response is acceptable (adequate).

REVIEWER'S OVERALL COMMENTS REGARDING NOVUM: All of the findings that are reported in the FORM FDA-483 were reviewed for their impact on ANDA #202121. It was found that the firm used actual blood sampling times, while the

reviewer used nominal sampling times. Importantly, sampling time deviations had no significant impact on the overall outcome of the BE study results.

With regard to the issue of maintaining adequate case histories, the firm stated that they would conduct an intensive training with all applicable staff in order to ensure accurate transcription of data. For the issue of no documentation to indicate that the clocks used to document the time of drug administration are synchronized to the clocks used to document the time of blood sampling, the firm stated the following: "*We are confident that the clocks were synchronized and we followed our established procedures"*. Novum also added that they already revised their SOP to record verification of synchronization.

The DBE considers the firm's response to FORM 483 is **acceptable (adequate)**. From bioequivalent point of view, the fasting BE study is for ANDA #202121 is acceptable.

2. Clinical Site #2 (Fed): Biovail Contract Research

This is a review of the OSI Inspection Report for the inspection of the clinical site, Biovail Contract Research (a division of Biovail Corporation) [DARRTS NDA (b) (4) MADA, SRIPAL R 11/10/2009 N/A 11/10/2009 CONSULT REV-BIOEQ-01(General Consult Review) Original-1 (Type 3- New Dosage Form) Archive]. Biovail was inspected on (b) (4) for NDA (b) (4) and the outcome was VAI. The OSI inspection was involved in both the clinical and analytical portions of the study. However, all deficiency items reported in the form FDA-483 were related to the analytical portion of the study. These items listed in the form FDA-483 were the following:

1. (b) (4)
2.
3.
4.

REVIEWER'S OVERALL COMMENTS REGARDING BIOVAIL: Biovail was used only as a clinical site for ANDA #202121. Therefore, the aforementioned items listed in the form FDA-483 regarding the analytical portion of the study do not relate to ANDA #202121.

There are no pending OSI inspections for this site. The clinical study is **acceptable (adequate)**.

3. Analytical Site (Fasting and Fed): (b) (4)

This is a review of the OSI Inspection Report for the inspection of the analytical site, (b) (4) [DARRTS NDA (b) (4) DASGUPTA, ARINDAM 03/02/2011 N/A 03/02/2011 CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Not Applicable) Archive]. (b) (4) was inspected on (b) (4) for ANDA (b) (4) and the outcome was VAI with a single item listed in the form FDA-483. To date there is no DBE review of the OSI finding (as of September 8, 2011). The impact of this finding on the current ANDA is reviewed below.

(b) (4)

OSI Conclusions: Following the above inspection, the Division of Scientific Investigations recommends the following:

- The analytical data of the studies CRI-00016842 and CRI-00016843 can be accepted for Agency review.

REVIEWER'S OVERALL COMMENTS REGARDING (b) (4): With regard to ANDA #202121, the reviewer checked to see if a single stock of progesterone and (b) (4) (IS) was used for both the method validation and during the fasting and fed BE studies. According to the report (see table 1 below), there were separate primary stocks made of the analyte and internal standard (IS) for the validation and during the study. From these primary stocks, single stocks of IS and QCs were made separately for both the fasting and fed BE studies. These IS/QC stock solutions were used for the entire fasting and fed BE studies, respectively. The primary stock stability, as well as the standards and QC sample long term storage stability (LTSS) data cover the storage durations for these BE studies (see Table 1 and Table 2 below).

Table 1: Different primary stock solutions were used for the method validation and during the fasting and fed BE studies. The stock stability data support the storage durations for the progesterone and IS primary stocks.

Analyte	Method Validation Primary Stock Solution Creation Dates	Analytical Report Primary Stock Solution Creation Dates	Standards and QC Sample Creation Date (primary stock solution spiked into stripped human plasma)	Primary Stock Stability according to Validation Report	Duration of Primary Stock in Storage	Does Primary stock stability cover the storage duration of the stock solutions?
Fasting BE Study						
Progesterone	08/27/2009	02/10/2010	02/25/2010	29 days	02/10/2010 to 02/25/2010 = 15 days	YES
(b) (4) (IS)	08/27/2009	02/22/2010		113 days	02/22/2010 to 02/25/2010 = 3 days	YES
Fed BE Study						
Progesterone	01/14/2010	03/15/2010	03/25/2010	29 days	03/15/2010 to 03/25/2010 = 10 days	YES
(b) (4) (IS)	11/18/2009	02/22/2010		113 days	02/22/2010 to 03/25/2010 = 32 days	YES

Table 2: The long term storage stability data covers the storage duration of the standards and QC samples for both the fasting and fed BE studies.

Analyte	Standards and QC Sample Creation Date	Last Day of Sample Analysis	Duration of Standards and QC Samples in Storage	Storage Stability (LTSS)	Does LTSS cover the storage duration?
Progesterone and (b) (4) (IS)	Fasting: 02/25/2010	03/19/2010	02/25/2010 to 03/19/2010 = 23 days	124 days	YES
	Fed: 03/25/2010	05/12/2010	03/25/2010 to 05/12/2010 = 49 days		

In addition, the accuracy of the method used for ANDA #202121 was assessed by comparing the reference product (PROMETRIUM®) results between similar ANDAs. For simplicity, only fasting studies were compared. As one can see from Table 3, the results between the two fasting studies carried out using plasma for matrix are similar, suggesting the method used in ANDA #202121 is accurate.

Table 3: Comparison of arithmetic means for reference product (PROMETRIUM®) from similar ANDAs:

ANDA #	Firm	Analytical Site	Method	Matrix	Study Type	Cmax (ng/mL)	Tmax (hr)**	AUC0-t (hr*ng/mL)	AUC∞ (hr*ng/mL)
202121	Teva	(b) (4)	Liquid-liquid extraction and derivatization step followed by LC and MS	Plasma	Fasting	6.40	2	20.98	28.33
									(b) (4)

**Median

In summary, OSI raised concern over (b) (4) use of single QC and calibration standard stocks for both method validation and during study analyses. However, this is not the case for the current ANDA because separate primary stock solutions of analyte and IS were made for the method validation and during the fasting and fed BE study analysis. Indeed, the firm did use the same calibration standard and QC samples throughout the studies, but this is acceptable practice. Furthermore, all of the stock solutions were supported by stability data (see Tables 1 and 2 above). Finally, the accuracy of the method used is validated by comparison with similar ANDA using a comparable method.

Taken together, this reviewer feels that the OSI finding does not impact the fasting and fed BE studies for ANDA #202121, and the firm's response is acceptable (adequate). **However, other ANDAs pending this VAI finding for (b) (4) should (1) determine if a single stock solution is used for their study and (2) determine the accuracy of the analytical method by comparing the pharmacokinetic results with similar ANDAs.**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202121

APPLICANT: Teva Pharmaceuticals, USA

DRUG PRODUCT: Progesterone Capsule, 100 mg and 200 mg

The Division of Bioequivalence (DBE) has completed its review of your amendment submission dated August 26, 2011, and has no further questions at this time.

The DBE acknowledges that you will continue to use the following dissolution method and specification in the dissolution testing of your product:

Media:	4.0 % of SLS Phosphate Buffer pH 6.8*
Volume:	250 mL
Temperature:	37 °C ± 0.5 °C
USP Apparatus:	III (Reciprocating Cylinder)
Top Screen:	30 mesh
Bottom Screen:	40 mesh
Sinker:	yes
Speed:	30 dip/minute
Specification:	NLT (b) (4) (Q) dissolved in 45 minutes

*To avoid excess foam formation, two drops of simethicone should be added.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

6 OUTCOME PAGE

ANDA: 202121

7 *COMPLETED ASSIGNMENT FOR 202121 ID: 15009*

Reviewer: DeHaven, Wayne **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Progesterone Capsule, 100 mg and 200 mg (Amendment and OSI)

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15009	8/26/2011	Other	Study Amendment	1	1
15009	(b) (4)	Other	DSI Inspection Report	1	1
15009		Other	DSI Inspection Report	1	1
15009		Other	DSI Inspection Report	0	0
				Bean Total:	3

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/s/

WAYNE I DEHAVEN
09/19/2011

SHRINIWAS G NERURKAR
09/19/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/25/2011