CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090410

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	90410	
Drug Product Name	Budesonide Capsules	
Strength (s)	3 mg	
Applicant Name	Mylan Pharmaceuticals Inc.	
Address	781 Chestnut Ridge Road, P.O. Box 4310, Morgantown, WV 26504-4310, USA	
Applicant's Point of Contact	S. Wayne Talton	
Contact's Phone Number	(304) 599-2595	
Contact's Fax Number	(304) 285-6407	
Submission Date(s)	March 12, 2008	
First Generic	No	
Reviewer	Svetlana Cherstniakova, Ph.D.	
Study Number (s)	BUDE-0722	BA07101140
Study Type (s)	Fasting	Fed
Strength(s)	3 mg	(b) (4)
Clinical Site	PRACS Institute, Ltd-Cetero Research	
Clinical Site Address	625 Demers Avenue East Grand Forks, MN 56721 USA	
Analytical Site	Mylan Pharmaceuticals Inc.	
Analytical Address	Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505	
OUTCOME DECISION	INCOMPLETE	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There are no USP and no FDA-recommended methods for this product. The firm conducted dissolution testing with its own proposed method. The firm's proposed dissolution method is acceptable. However the firm's proposed specifications are not acceptable. Based on the submitted dissolution data, the DBE proposes the following specifications. The firm should acknowledge the following dissolution testing method and specifications:

Apparatus:	USP Apparatus 2 (paddle)	
Medium:	Acid stage: 0.1 N HCl	
	Buffer stage: pH 6.8 Phosphate Buffer	
Volume:	500 mL for acid stage and 500 mL for buffer stage	
Specifications:	Acid stage:	NMT (b) (4) of labeled content after 2 hrs.
	Buffer stage:	1 hour (b) (4) of labeled content
		2 hours (b) (4) of labeled content
		6 hours NLT (b) (4) of the labeled content

The DBE will review the fasted and fed BE studies at a later date.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

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 an 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.					

Background on Dissolution Testing for Budesonide Capsules: NOT TO BE RELEASED UNDER FOI

1. Based on the OCPB review of clinical pharmacology and biopharmaceutics data submitted under the NDA 21324 (DFS 021324 N 000 C 30-Mar-2001) by the AstraZeneca for their product, Entocort™ (budesonide capsules), the *in vitro* dissolution of budesonide was tested in simulated gastric (pH 1.2) and intestinal (pH 7.5) fluids at 37ºC using a flow through cell methodology [Wennergren et al., Int. J. Pharm; 1989; 53: 35 – 41]. The dissolution method and specifications for Entocort™ capsules, 3 mg, is as follows:

Apparatus: USP Apparatus 4 with 12 mm flow-through cells at 8 ml/min at 37ºC
Performed on one composite sample consisting of the contents from 8 capsules
Medium: Acid stage: SGF, pH 1.2; Buffer stage: SIF, pH 7.5
Specifications: Acid stage: NMT (b) (4) of labeled content after 2 hrs.
Buffer stage: After 1 hr (b) (4) of labeled content

After 2 hr [redacted] of labeled content
After 4 hr [redacted] of labeled content
After 8 hr NLT [redacted] of the labeled content

2. In the recent control correspondence OGD #07-1086 [redacted] dated 10/16/2007, the OGD provides following recommendations regarding dissolution testing of Budesonide Capsules, 3 mg:

Please develop a discriminating dissolution method for your proposed budesonide capsules. The formulation of the RLD is designed to protect dissolution in gastric juice, but dissolve at pH > 5.5. Your product should have similar characteristics. You should develop a dissolution method comprised of an acid stage and a buffer stage. In addition, please try the method published in Wennergren et al., Int. J. Pharm. 1989; 53: 35 – 41, with your product.

3. The DBE has reviewed dissolution data for the only genetic version of this drug product submitted in support of ANDA [redacted] conducted dissolution testing with its own proposed method. Based on a review of the dissolution testing data of ANDA [redacted] see DFS N [redacted] N 000 31-Jan-2008), the DBE agreed with the following dissolution method for Budesonide Enteric Coated Capsule, 3 mg:

Apparatus:	USP Apparatus 2 (Paddle), with capsule sinker		
Rotation speed	75 rpm		
Medium	**Temperature**: 37°C		**Volume**
First 2 hours;	Acid stage	0.1 N HCl	1000 mL
2-10 hours	Buffer stage	Phosphate Buffer, pH 7.5	1000 mL
Sampling times			
Acid stage	2 Hours		
Buffer stage	1, 2, 4, 6,and 8 hours		

Specifications:

Acid stage

Time (hours)	% Budesonide Dissolved
2	NMT [redacted]

Buffer stage:

Time (hours)	% Budesonide Dissolved
1	[redacted]
2	
4	
6	NLT [redacted]

In the current application, the firm conducted dissolution testing with its own proposed method. The firm's dissolution method and data are summarized below (Table 2).

Mylan's dissolution method is similar to that used in [redacted]ANDA [redacted]with a noticeable difference in the rotational speed (100 rpm Mylan's method vs 75 rpm in [redacted]). However, while the [redacted]method uses 1000 mL of dissolution media, Mylan's method used only 500 mL in each case (acid and buffer stages).

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	**2 (paddles)**
	Speed of Rotation:	**100 rpm**
	Medium:	**0.1 N HCl (Acid Stage), pH 6.8 Phosphate Buffer (Buffer Stage)**
	Volume:	**500 mL (Acid Stage), 500 mL (Buffer Stage)**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**Acid Stage: NMT (b) (4) in 2 hours Buffer Stage : (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) in 9 hours**	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	**Testing Date**	**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**
						Acid Stage	**Buffer Stage**						
						2 hours	**1 hour**	**2 hours**	**4 hours**	**6 hours**	**9 hours**	**12 hours**	
N/A	10/31/07	Budesonide Capsules Lot 1000093 Manufacture Date – 08/07/07	3 mg Capsules	12	Mean	0%	53%	72%	87%	92%	95%	95%	3.2.P.5.4 Batch Analysis
					Range	(b) (4)							
					%CV	0.0%	10.6%	8.3%	4.8%	3.0%	2.9%	2.7%	
N/A	11/02/07	Entocort® EC Capsules Lot MP0078 Expiration Date – 08/09	3 mg Capsules	12	Mean	0%	53%	70%	86%	92%	94%	94%	
					Range	(b) (4)							
					%CV	0.0%	9.8%	7.4%	3.2%	1.4%	1.4%	1.6%	

II. COMMENTS:

The firm's proposed dissolution method is acceptable. However the firm's proposed specifications are not acceptable. Based on the submitted dissolution data, the DBE proposes the following specifications. The firm should acknowledge the following dissolution testing method and specifications. The dissolution testing should be conducted as follows:

Apparatus: USP Apparatus 2 (paddle)
Medium: Acid stage: 0.1 N HCl
Buffer stage: pH 6.8 Phosphate Buffer
Volume: 500 mL for acid stage and 500 mL for buffer stage
Specifications: Acid stage: NMT (b) (4) of labeled content after 2 hrs.
Buffer stage: 1 hour (b) (4) of labeled content
2 hours (b) (4) of labeled content
6 hours NLT (b) (4) of the labeled content

III. DEFICIENCY COMMENTS:

The firm should acknowledge the following dissolution testing method and specifications. The dissolution testing should be conducted as follows:

Apparatus: USP Apparatus 2 (paddle)
Medium: Acid stage: 0.1 N HCl
Buffer stage: pH 6.8 Phosphate Buffer
Volume: 500 mL for acid stage and 500 mL for buffer stage
Specifications: Acid stage: NMT (b) (4) of labeled content after 2 hrs.
Buffer stage: 1 hour (b) (4) of labeled content
2 hours (b) (4) of labeled content
6 hours NLT (b) (4) of the labeled content

IV. RECOMMENDATIONS:

The firm's proposed dissolution method is acceptable. However the firm's proposed specifications are not acceptable. The firm should acknowledge the dissolution testing method and specifications described above.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 90410

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Budesonide Capsules, 3 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 bioequivalence studies will be conducted later. The following deficiency has been identified:

Your dissolution method is acceptable. However, your proposed specifications are not acceptable. Please acknowledge the following dissolution testing method and specifications. The dissolution testing should be conducted as follows:

Apparatus: USP Apparatus 2 (paddle)
Medium: Acid stage: 0.1 N HCl
Buffer stage: pH 6.8 Phosphate Buffer
Volume: 500 mL for acid stage and buffer stage
Specifications: Acid stage: NMT (b) (4) in 2 hours.
Buffer stage:
1 hour (b) (4) of labeled content
2 hours of labeled content
6 hours NLT (b) (4) of the labeled content

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

ANDA: 90410

VI. *Completed Assignment for 90410 ID: 5933*

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5933	3/12/2008	Dissolution Data	Dissolution Review	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Review	
Dissolution Review	1
Dissolution Review 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/

Svetlana Cherstniakova
7/30/2008 02:25:00 PM
BIOPHARMACEUTICS

Chandra S. Chaurasia
7/31/2008 11:04:08 AM
BIOPHARMACEUTICS

Moheb H. Makary
7/31/2008 11:15:03 AM
BIOPHARMACEUTICS
For Dr. Barbara M. davit, Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	90-410
Drug Product Name	Budesonide Capsules
Strength(s)	3 mg
Applicant Name	Mylan pharmaceuticals, Inc.
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310
Applicant's Point of Contact	S. Wayne Talton
Contact's Telephone Number	304-599-2595
Contact's Fax Number	304-285-6407
Original Submission Date(s)	DATE OF APPLICATION: March 13, 2008 DATE (RECEIVED) ACCEPTABLE FOR FILING: March 13, 2008
Submission Date(s) of Amendment(s) Under Review	October 15, 2008 (Dissolution Acknowledgement)
Reviewer	Suman Dandamudi
Study Number (s)	BUDE-0722
Study Type (s)	A randomized, two-Way crossover, single-dose, open-label study under fasted conditions in healthy, healthy subjects.
Strength (s)	3 mg
Clinical Site	PRACS Institute Ltd-Cetero Research
Clinical Site Address	625 Demers Avenue East Grand Forks, MN 56721 USA
Analytical Site	Mylan Pharmaceuticals Inc.
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505
Study Number (s)	BUDE-0802
Study Type (s)	A randomized, two-Way crossover, single-dose, open-label study under fed conditions in healthy subjects.
Strength (s)	3 mg
Clinical Site	PRACS Institute Ltd-Cetero Research
Clinical Site Address	625 Demers Avenue East Grand Forks, MN 56721 USA
Analytical Site	Mylan Pharmaceuticals Inc.
Analytical Site Address	Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505
OUTCOME DECISION	**INCOMPLETE**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Budesonide Capsules, 3 mg, to the corresponding reference product, AstraZeneca, ENTOCORT EC® (Budesonide) Capsules, 3 mg. Each of the BE studies were designed as a single-dose, two-way crossover study in healthy subjects.

However the firm's fasting and fed BE studies are incomplete due to deficiencies related to the clinical and analytical parts of the study. The firm did not provide individual PK parameters and mean budesonide concentrations over time plots (linear and semilog) for both the treatments of both fasting and fed studies. The firm also did not submit the statistical report of both the BE studies. In addition, the firm did not specify the form of EDTA (anticoagulant) used in the pre-study validation.

The firm has conducted acceptable comparative dissolution testing on Budesonide Capsules, using its own proposed dissolution method (DARRTS: dissolution review of ANDA 90410). On 10/15/2008, the firm has acknowledged the FDA-recommended dissolution specification. The dissolution testing is complete.

The clinical site was inspected on 9/14/2006. The analytical site was inspected on 9/26/2007. No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[1, 2]

Test Product	Budesonide Capsules, 3 mg
Reference Product	ENTOCORT EC® (Budesonide) Capsules, 3 mg
RLD Manufacturer	AstraZeneca
NDA No.	021324
RLD Approval Date	October 2, 2001
Indication	• For the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. • For the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.

[1] Online-Orange Book (2009). http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
[2] Labeling for the RLD Product

3.2 PK/PD Information[2, 3, 4]

Bioavailability	The absorption of ENTOCORT EC® seems to be complete, although Cmax and Tmax are variable. The systemic availability after a single dose is higher in patients with Crohn's disease compared to healthy volunteers (21% vs 9%) but approaches that in healthy volunteers after repeated dosing.
Food Effect	A mean delay in time to peak concentration of 2.5 hours is observed with the intake of high-fat meal with no significant differences in AUC
Tmax	Time to peak concentration varies in individual patients between 30 and 600 minutes.
Metabolism	Budesonide undergoes approximately 85% first pass metabolism to two inactive metabolites: 16alpha-hdroxyprednisolone (24%) and 6beta-hydroxybudesonide (5%).
Excretion	Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [3H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.
Half-life	The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2.0 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.
Drug Specific Issues (if any)	Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Glucocorticosteroids are secreted in human milk. The amount of budesonide secreted in breast milk has not been determined. Caution should be taken in patients with tuberculosis, hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

[3] Online-Clinical Pharmacology (2009). http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=585

[4] http://www.rxlist.com/script/main/hp.asp

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover *in vivo*
	Strength:	3 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	3 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Budesonide in plasma
Bioequivalence based on:	90% CI of Budesonide
Waiver request of in-vivo testing:	N/A
Source of most recent recommendations:	Control Document 04-710 (Mylan; 7/14/2004, OGD letter date 09/29/2004) and 08-0317 ((b) (4) 03/07/2008)
Summary of OGD or DBE History	There are no approved ANDAs for Budesonide Capsules in Orange Book ANDAs which are under review ANDA # (b) (4)

3.4 Contents of Submission

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

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation Report location	Budesonide Bioanalytical Method Validation Report, Sections 5.3.1.4. See Budesonide Validation Addendum 2 Table 2.
Analyte	Budesonide
Internal standard (IS)	(b) (4)
Method description	Liquid/Liquid; LC/MS/MS – APCI
Limit of quantitation	0.3 ng/mL(Range I) [a] 0.1 ng/mL (Range II) [b]
% recovery (and %CV) at each concentration tested	0.9 ng/mL- 72.96%, %CV= 3.07 3 ng/mL- 77.22%, %CV= 2.44 24 ng/mL- 84.15%, %CV= 5.26 [a]
Average recovery of IS (%)	73.53%, %CV= 1.40 [a]
Standard curve concentrations (ng/mL)	0.3, 0.45, 0.6, 0.9, 1.5, 3, 6, 12, 27, 30 ng/mL(Range I) [a] 0.1, 0.2, 0.3, 0.4, 0.5, 1, 1.5, 3, 4.5, 5 ng/mL (Range II) [b]
QC concentrations (ng/mL)	0.9, 3, 24 ng/mL (Range I) [a] 0.3, 1, 4 ng/mL (Range II) [b]
QC Intraday precision range (%)	1.39% to 4.24% (Range I) [a] 1.10% to 5.45% (Range II) [b]
QC Intraday accuracy range (%)	-5.38% to 8.13% (Range I) [a] -6.31% to 3.80% (Range II) [b]
QC Interday precision range (%)	3.50% to 5.13% (Range I) [a] 2.11% to 5.05% (Range II) [b]
QC Interday accuracy range (%)	-2.23% to 1.63% (Range I) [a] -3.03% to 2.53% (Range II) [b]
Bench-top stability (hrs)	9.5 hours @ room temperature [a]
Stock stability (days)	BUDE - SS 12 days @ 4°C [a] BUDE - WS 12 days @ 4°C (Range I) [a] BUDE - WS 11 days @ 4°C (Range II) [b] (b) (4) - SS 11 days @ 4°C [a] - WS 11 days @ 4°C [a]
Processed stability (hrs)	98.25 hours @ room temperature [a]
Freeze-thaw stability (cycles)	3 cycles [a]
Long-term storage stability (days)	3 days @ -70°C - frozen stability on-going (Range I) [a] 51 days @ -70°C and -15°C (Range II) [c]
Dilution integrity	Concentration diluted five-fold [b]
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes
Bioanalytical method is acceptable	Incomplete

[a]Generated in BUDE VALI, [b] Generated in BUDE VALI Addendum 1,
[c]Generated in BUDE VALI Addendum 2

Comments on the Pre-Study Method Validation:

- The long term storage data of 51 days exceed the storage period for the samples of both the fasted (38 days) and fed (25 days) BE studies.

- The firm did not specify the form of EDTA (i.e K2-EDTA or K3-EDTA) used in the conductance of pre-study validation.

- The pre-study validation data are incomplete.

3.6 In Vivo Studies

Table 1. Summary of all *in vivo* Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (Range)	Mean Parameters (± SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hour /mL)	AUC_{∞} (ng*hour /mL)	T½ (hr)	K_{el} (hr-1)	
Study # BUDE-0722	Single-Dose Fasting Bioequivalence Study of Budesonide Capsules (3 mg; Mylan) and Entocort® EC Capsules (3 mg; AstraZeneca) in Healthy Volunteers	Open-Label, Single-Dose, Randomized, Two-Period, Two-Treatment Crossover, bioequivalence study	**Test product** Oral Budesonide, 3 mg Capsules Mylan Pharmaceuticals Lot No. 1000093 Exp. Date N/A	56 Dosed 55 Completed 54 Analyzed Healthy Subjects Males-23 Females-31 Mean Age: 32 years (Range: 18 to 56 yrs)	Mean= 1.38 SD= 1.00	Median = 4.5 Range: 1.5-10.0	Mean= 10.13 SD = 7.02	Mean= 11.49* SD = 7.65	Mean= 5.68* SD = 2.16	Mean= 0.137* SD = 0.0475	**Module 5, Section 5.3.1.2**
			Ref. Product Oral ENTOCORT EC® (Budesonide) 3 mg Capsules, Astrazeneca Lot No. MP0078 Exp. Date: August 31, 2009		Mean= 1.27 SD = 0.90	Median = 4.5 Range: 2.0-6.5	Mean= 9.51 SD = 6.57	Mean= 10.99 SD = 7.44	Mean= 6.22 SD = 2.70	Mean= 0.130 SD = 0.0493	
Study # BUDE-0802	Single-Dose Fed Bioequivalence Study of Budesonide Capsules (3 mg; Mylan) and Entocort® EC Capsules (3 mg; AstraZeneca) in Healthy Volunteers	Open-Label, Single-Dose, Randomized, Two-Period, Two-Treatment Crossover, bioequivalence study	**Test product** Oral Budesonide, 3 mg Capsules Mylan Pharmaceuticals Lot No. 1000093 Exp. Date N/A	64 Dosed 62 Completed 62 Analyzed Healthy Subjects Males-32 Females-30 Mean Age: 27 years (Range: 18 to 62 yrs)	Mean= 1.66 SD = 1.00	Median = 6.5 Range: 4.0-24.0	Mean= 11.29 SD = 6.43	Mean= 12.89# SD = 7.17	Mean= 6.46# SD = 1.74	Mean= 0.117# SD = 0.0430	**Module 5, Section 5.3.1.2**
			Ref. Product Oral ENTOCORT EC® (Budesonide) 3 mg Capsules, Astrazeneca Lot No. MP0078 Exp. Date: August 31, 2009		Mean= 1.79 SD = 1.12	Median = 6.5 Range: 4.0-24.0	Mean= 11.66 SD = 6.49	Mean= 13.36** SD = 7.21	Mean= 6.03** SD = 1.56	Mean= 0.124** SD = 0.0396	

*n=52, # n=57, ** n= 61

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

The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax will be calculated by the reviewer after the firm responds to the deficiency comments.

Table 3. Reanalysis of Study Samples

Fasted Study, Study No. BUDE-0722								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	R	T	R	T	R	T	R	T
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Reason A[1]	1	1	0.04	0.04	1	1	0.04	0.04
Total	1	1	0.04	0.04	1	1	0.04	0.04
Fed Study, Study No. BUDE-0802								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	R	T	R	T	R	T	R	T
Pharmacokinetic	0	0	0.0	0.0	0	0	0.0	0.0
Reason A[1]	3	1	0.11	0.04	3	1	0.11	0.04
Reason B[2]	0	2	0.00	0.07	0	2	0.00	0.07
Reason C[3]	1	0	0.04	0.00	1	0	0.04	0.00
Total	4	3	0.14	0.11	4	3	0.14	0.11

Fasted study: 1- Abnormal Internal Standard Response
Fed Study: 1- Documented Sample Processing Error
2- Sample Outside Limits of Curve Range (ALQ)
3- Abnormal Internal Standard Response

Comments from the Reviewer:

The firm reassayed the study samples because of the analytical reasons "Abnormal Internal Standard Response", "Documented Sample Processing Error" and "Sample Outside Limits of Curve Range (ALQ)". The SOP's of sample re-analysis were provided and are acceptable.

3.7 Formulation

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

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DARRTS: Dissolution review of ANDA 90410
Source of Method (USP, FDA or Firm)	Firm
Medium	Acid stage: 0.1 N HCl Buffer stage: pH 6.8 Phosphate Buffer
Volume (mL)	500 mL for acid stage and 500 mL for buffer stage
USP Apparatus type	II (Paddle)
Rotation (rpm)	100 rpm
DBE-recommended specifications	**Acid stage:** NMT (b) (4) of labeled content after 2 hrs. **Buffer stage:** 1 hour (b) (4) of labeled content 2 hours (b) (4) of labeled content 6 hours NLT (b) (4) of the labeled content
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Enteric coated
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	N/A

Reviewer's notes:

There is no USP method, but there is a FDA-recommended method for this product. However, the firm conducted dissolution testing with its own proposed method. This is acceptable since the firm conducted the study prior to the FDA-recommended dissolution method being posted in the FDA website. The firm's initially proposed specification of "Acid Stage: NMT (b) (4) in 2 hours, Buffer Stage: (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) in 9 hours" was not acceptable. DBE requested the firm to acknowledge the FDA-recommended specification of "Acid Stage: NMT (b) (4) in 2 hours, Buffer Stage: (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) in 6 hours". In its amendment dated on 10/15/2008, the firm acknowledged the FDA-recommended dissolution specification. The dissolution testing is acceptable.

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested *in vivo*?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

3.10 Deficiency Comments

1. The firm did not specify the form of EDTA used in the conductance of pre-study validation. The firm should confirm whether the anticoagulant (K2 EDTA) was used to prepare standard, quality control and stability samples of the pre-study method validation as well as the standard and quality controls of the during-study method validation. Per firm's study report, the subject plasma samples were collected in this anticoagulant (K2 EDTA).

2. The firm should submit the individual pharmacokinetic parameters for budesonide of all the subjects for both fasting and fed BE studies. In addition the firm also should submit the linear and semi-log plots of the mean budesonide concentrations over time for both the treatments of both fasting and fed BE studies.

3. The firm should submit the statistical report of both the fasting and fed BE studies.

4. In the Table 6 of the bioanalytical report (Module 5.3.1.4) it was stated that plasma samples of the Subject 4 were not received by the analytical site. The SAS data the firm provided contains the budesonide concentrations at all time points in both the periods for subject 4. However the plasma concentrations of budesonide for subject 10 were missing from both the periods. The firm should clarify the discrepancy observed in the missing subject samples.

3.11 Recommendations

1. The Division of Bioequivalence finds the fasting BE study No. BUDE-0722 conducted by the Mylan Pharmaceuticals, Inc on its Budesonide Capsules, 3 mg, lot # 1000093, comparing it to AstraZeneca's ENTOCORT EC® (Budesonide) Capsules, 3 mg, lot # MP0078, incomplete due to the deficiencies mentioned above.

2. The Division of Bioequivalence finds the fed BE study No. BUDE-0802 conducted by the Mylan Pharmaceuticals, Inc on its Budesonide Capsules, 3 mg, lot # 1000093,

comparing it to AstraZeneca's ENTOCORT EC® (Budesonide) Capsules, 3 mg, lot # MP0078, incomplete due to the deficiencies mentioned above.

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted using the following method:

Apparatus:	USP Apparatus 2 (paddle)
Medium:	Acid stage: 0.1 N HCl
Buffer stage:	pH 6.8 Phosphate Buffer
Volume:	500 mL for acid stage and 500 mL for buffer stage
Specifications:	Acid stage: NMT (b) (4) of labeled content after 2 hrs.
	Buffer stage: 1 hour (b) (4) of labeled content
	2 hours (b) (4) of labeled content
	6 hours NLT (b) (4) of the labeled content

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	BUDE-0722
Study Title	Single-Dose Fasting Bioequivalence Study of Budesonide Capsules (3 mg; Mylan) and Entocort® EC Capsules (3 mg; AstraZeneca) in Healthy Volunteers
Clinical Site (Name & Address)	PRACS Institute, Ltd-Cetero Research 625 Demers Avenue East Grand Forks, MN 56721 USA 701-239-4750
Principal Investigator	Alan K. Copa, PharmD
Dosing Dates	Period I: 10-Nov-2007 Period II: 17-Nov-2007
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505 800-826-9526
Analysis Dates	Budesonide: 29-Nov-2007 to 18-Dec-2007
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)	Budesonide: Aliquot 1: 38 Days @ -70°C Aliquot 2: 38 Days @ -70°C Date of 1st Sample Collected: 10-Nov-2007 Date of Last Sample Extracted: 18- Dec-2007

Table 5. Product information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Budesonide Capsules	ENTOCORT EC® Capsules
Manufacturer	Mylan Pharmaceuticals, Inc.	AstraZeneca
Batch/Lot No.	1000093	MP0078
Manufacture Date	10/16/2007	
Expiration Date		8/31/2009
Strength	3 mg	3 mg
Dosage Form	Capsules	Capsules
Bio-Batch Size	152,072	
Production Batch Size	(b) (4)	
Potency (Assay)	100.9%	101.9%
Content Uniformity (mean, %CV)	100.3% (1.8%)	102.6% (1.6%)
Dose Administered	3 x 3 mg	3 x 3 mg
Route of Administration	Oral	Oral

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

Number of Subjects	56 enrolled 55 completed 54 analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 02, 04, 05, 07, 09, 12, 16, 17, 18, 19, 21, 22, 27, 29, 30, 33, 34, 36, 37, 38, 42, 45, 47, 48, 51, 52, 53, 55 BA: 01, 03, 06, 08, 10, 11, 13, 14, 15, 20, 23, 24, 25, 26, 28, 31, 32, 35, 39, 40, 41, 43, 44, 46, 49, 50, 54, 56
Blood Sampling Times	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16, 20 and 24 hours post dose
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K2 EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C to separate plasma. Plasma samples were divided equally into two aliquots and immediately frozen at -70° C ± 15° C for storage and later analysis
IRB Approval	Approved on 10/03/2007; protocol amendment and revisions to the consent form were approved on 10/26/2007.
Informed Consent	Yes
Length of Fasting	Ten hours prior to dosing and additional 4 hours after dosing
Length of Confinement	On the day of each study day and 24 hours following each dose
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured throughout the study.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. BUDE-0722			
		Treatment Groups	
		Test Product N =55	Reference Product N =55
Age (years)	Mean ± SD	32.04 ± 12.53	32.04 ± 12.53
	Range	18 – 56	18 – 56
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	40 (72.73%)	40 (72.73%)
	40 – 64	15 (27.2%)	15 (27.2%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	23 (41.82%)	23 (41.82%)
	Female	32 (58.18%)	32 (58.18%)
Race (Hispanic or Latino)	N	0 (0%)	0 (0%)
	A	0 (0%)	0 (0%)
	B	0 (0%)	0 (0%)
	I	0 (0%)	0 (0%)
	W	0 (0%)	0 (0%)
Race (Not Hispanic or Latino)	N	1 (1.82%)	1 (1.82%)
	A	0 (0%)	0 (0%)
	B	1 (1.82%)	1 (1.82%)
	I	0 (0%)	0 (0%)
	W	53 (96.36%)	53 (96.36%)
BMI (Kg/m^2)	Mean + SD	24.89 ± 2.67	24.89 ± 2.67
	Range	20.4 – 30.2	20.4 – 30.2
Other Factors			

RACE	
American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
43	Subject dropped per sponsor due to adverse event (vomiting) prior to Period II check-in.	I	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System /Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BUDE-0722	
	Test (N=55)	Reference (N=56)
Gastrointestinal disorders		
Nausea	0 (0.00%)	1 (1.79%)
Vomiting	0 (0.00%)	1 (1.79%)
Infections and infestations		
Sinusitis	0 (0.00%)	1 (1.79%)
Injury, poisoning and procedural complications		
Vertebral injury	0 (0.00%)	1 (1.79%)
Nervous system disorder		
Headache	3 (5.45%)	2 (3.57%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	0 (0.00%)	1 (1.79%)
Pharyngolaryngeal pain	0 (0.00%)	1 (1.79%)
Total Subjects Reporting at Least One Adverse Event	**3 (5.45%)**	**4 (7.14%)**

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. BUDE-0722		
Type	**Subject (Test)**	**Subject (Ref.)**
Concomitant medications	09, 37, 53	11, 43, 54
Blood sample collection time deviations	03, 04, 06, 10, 11, 17, 18, 27, 42	04, 10, 11, 35, 36, 43, 56
Missed blood sample collections	10	04
Meal requirement violation: Consumed less than 75% of Period I check-in dinner (subjects 07, 48, 56)	N/A	N/A
Meal requirement violation: Consumed less than 75% of Period I lunch	07, 48	N/A
Meal requirement violation: Consumed less than 75% of Period I dinner	07, 48, 52	08, 13
Meal requirement violation: Consumed less than 75% of Period II check-in dinner (subjects 07, 08, 26, 29, and 56)	N/A	N/A
Meal requirement violation: Consumed less than 75% of Period II lunch	N/A	07, 48
Meal requirement violation: Consumed less than 75% of Period II dinner	01, 35	07, 48, 53

Comments on Dropouts/Adverse Events/Protocol Deviations:

Dropouts and Adverse Events: Subject 43 (Period I) who received Reference, experienced vomiting at 12.33 hours. The firm stated that the severity of the condition was moderate and the effect was observed after 2X median of Tmax. However the firm dropped subject 43 prior to period II check in.

Protocol Deviations:

- The firm stated that for Subject 10 in Period II, the blood sample could not be collected at time points 6 and 16 hours. So the firm dropped this subject from the analysis.
- There were some blood sampling deviations during fasting bioequivalence study. However, these sampling time deviations are minor deviations which occurred in less than 5% of the nominal time points, thus are considered to be insignificant. The firm used actual sampling times for its PK calculation.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. BUDE-0722 Budesonide										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1	0.2	0.3	0.4	0.5	1.0	1.5	3.0	4.5	5.0
Inter day Precision (%CV)	1.43	2.75	3.19	2.70	3.11	2.80	3.46	2.67	1.99	2.74
Inter day Accuracy (%Actual)	100.60	99.35	99.60	99.82	98.58	101.30	100.40	100.00	100.62	99.68
Linearity	0.9921-0.9997									
Linearity Range (ng/mL)	0.1-5.0 ng/mL									
Sensitivity/LOQ (ng/mL)	0.1 ng/mL									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3	1.0	4.0	4.0 diluted
Inter day Precision (%CV)	4.17	3.88	4.59	NA
Inter day Accuracy (%Actual)	99.37	99.18	99.68	NA

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

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

SOP No.	Effective Date of SOP	SOP Title
D-400-08	05/22/07	Reassay or Reinjection of Clinical Samples
D-416-05	10/19/06	Reassay of Whole Subjects

Table 13. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Pending the firm's submission of PK parameters and statistical report.

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

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. BUDE-0722				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	8.27	7.72	1.08	101.0-114.4
AUC∞ (ng *hr/mL)*	9.57	9.04	1.06	100.4-112.2
Cmax (ng/mL)	1.12	1.04	1.08	99.0-117.3

***N= 52**

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

Pending the firm's submission of PK parameters and statistical report.

Table 17. Additional Study Information

Pending the firm's submission of PK parameters and statistical report.

Comments on Pharmacokinetic and Statistical Analysis:

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax, **provided by the firm**, met the criteria for BE.

- The firm did not submit the individual pharmacokinetic parameters for budesonide of all the subjects. In addition the firm also did not submit the linear

and semi-log plots of the mean budesonide concentrations over time for both the treatments.

- The firm did not submit the statistical report of the fasting study.

- In the Table 6 of the bioanalytical report (Module 5.3.1.4) it was stated that plasma samples of the Subject 4 were not received by the analytical site. The SAS data files provided contains the budesonide concentrations at all time points in both the periods for subject 4. However, the plasma concentrations of budesonide for subject 10 were missing from both the periods. The firm should clarify the discrepancy observed in the missing subject samples.

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax will be calculated by the reviewer after the firm submits the responses to the deficiency comments.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

Incomplete.

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

Pending the firm's submission of PK parameters and statistical report.

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

Pending the firm's submission of PK parameters and statistical report.

4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	BUDE-0802
Study Title	Single-Dose Fed Bioequivalence Study of Budesonide Capsules (3 mg; Mylan) and Entocort® EC Capsules (3 mg; AstraZeneca) in Healthy Volunteers
Clinical Site (Name & Address)	PRACS Institute, Ltd-Cetero Research 625 Demers Avenue East Grand Forks, MN 56721 USA 701-239-4750
Principal Investigator	Alan K. Copa, PharmD
Dosing Dates	Period I: 19-Jan-2008 Period II: 26-Jan-2008
Analytical Site (Name & Address)	Mylan Pharmaceuticals Inc. Bioanalytical Department 3711 Collins Ferry Rd Morgantown, WV 26505 800-826-9526
Analysis Dates	Budesonide: 31-Jan-2008 to 13-Feb-2008
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)	Budesonide: Aliquot 1: 25 Days @ -70°C Date of 1st Sample Collected: 19-Jan-2008 Date of Last Sample Extracted: 13-Feb-2008

Table 20. Product Information

Product	Test	Reference
Treatment ID	Treatment A	Treatment B
Product Name	Budesonide Capsules	ENTOCORT EC® Capsules
Manufacturer	Mylan Pharmaceuticals, Inc.	AstraZeneca
Batch/Lot No.	1000093	MP0078
Manufacture Date	10/16/2007	
Expiration Date		8/31/2009
Strength	3 mg	3 mg
Dosage Form	Capsules	Capsules
Bio-Batch Size	152,072	
Production Batch Size	(b) (4)	
Potency (Assay)	100.9%	101.9%
Content Uniformity (mean, %CV)	100.3% (1.8%)	102.6% (1.6%)
Dose Administered	3 x 3 mg	3 x 3 mg
Route of Administration	Oral	Oral

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

No. of Subjects	64 enrolled and dosed 62 Analyzed
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 1, 4, 5, 6, 9, 12, 13, 16, 17, 18, 22, 23, 27, 28, 29, 30, 34, 36, 37, 39, 43, 44, 45, 48, 50, 52, 53, 56, 57, 60, 62, 63 BA: 2, 3, 7, 8, 10, 11, 14, 15, 19, 20, 21, 24, 25, 26, 31, 32, 33, 35, 38, 40, 41, 42, 46, 47, 49, 51, 54, 55, 58, 59, 61, 64
Blood Sampling Times	Predose, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 11, 12, 13, 14, 16, 20 and 24 hours post dose
Blood Volume Collected/Sample	10 mL
Blood Sample Processing/Storage	Blood samples were collected by direct venipuncture using pre-labeled vacutainers containing K2 EDTA as the anticoagulant. After blood collection, tubes were centrifuged at 3000 rpm for 10 minutes at 4° C to separate plasma. Plasma samples were divided equally into two aliquots and immediately frozen at -70° C ± 15° C for storage and later analysis
IRB Approval	Approved on 01/16/2008
Informed Consent	Yes
Length of Fasting Before Meal	The subjects were fasted 10 hours overnight. A standard high fat breakfast was given 30 minutes prior to dosing
Length of Confinement	On the day of each study day and 24 hours following each dose
Safety Monitoring	Adverse events were collected and reports were tabulated. The vital signs were measured through out the study.

Standard FDA Meal Used?	Yes

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics Profile of Subjects Completing the Bioequivalence Study

Fasting Bioequivalence Study No. BUDE-0802			
		Treatment Groups	
		Test Product N =62	Reference Product N =62
Age (years)	Mean ± SD	26.52 ± 11.00	26.52 ± 11.00
	Range	18 – 62	18 – 62
Age Groups	< 18	0 (0.0%)	0 (0.0%)
	18 – 39	52 (83.87%)	52 (83.87%)
	40 – 64	10 (16.13%)	10 (16.13%)
	65 – 75	0 (0.0%)	0 (0.0%)
	> 75	0 (0.0%)	0 (0.0%)
Sex	Male	32 (51.61%)	32 (51.61%)
	Female	30 (48.39%)	30 (48.39%)
Race (Hispanic or Latino)	N	0 (0%)	0 (0%)
	A	0 (0%)	0 (0%)
	B	0 (0%)	0 (0%)
	I	0 (0%)	0 (0%)
	W	1 (1.61%)	1 (1.61%)
Race (Not Hispanic or Latino)	N	0 (0%)	0 (0%)
	A	1 (1.61%)	1 (1.61%)
	B	1 (1.61%)	1 (1.61%)
	I	0 (0%)	0 (0%)
	W	59 (95.16%)	59 (95.16%)
BMI (Kg/m^2)	Mean + SD	25.66 ± 2.93	25.66 ± 2.93
	Range	19.9 – 30.9	19.9 – 30.9
Other Factors			

RACE	
American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
01	Dropped by the sponsor prior to Period II check-in due to an adverse event (vomited).	I	No
20	Elected to withdraw prior to Period II check-in due to personal reasons.	I	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System /Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. BUDE-0802	
	Test (N=63)	Reference (N=63)
Gastrointestinal disorders		
Abdominal pain	0 (0.00%)	1 (1.59%)
Stomach discomfort	1 (1.59%)	0 (0.00%)
Vomiting	1 (1.59%)	0 (0.00%)
General disorders and administration site conditions		
Vessel puncture site haematoma	0 (0.00%)	1 (1.59%)
Nervous system disorders		
Headache	1 (1.59%)	1 (1.59%)
Total Subjects Reporting at Least One Adverse Event	**2 (3.17%)**	**3 (4.76%)**

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medications	01	N/A
Blood sample collection time deviations	06, 16, 28, 29, 37, 39, 45, 50, 52, 55	06, 07, 16, 19, 20, 29, 38, 48, 50, 55
Exclusion Criteria – Ingestion of vitamins within 7 days prior to initial dose of study medication (Subject 6)	N/A	N/A
Exclusion Criteria – use of a tobacco containing product within 1 year of the study start date (Subject 36)	N/A	N/A
Inclusion Criteria – Body Mass Index (BMI) greater than 30 (Subject 33)	N/A	N/A

Other (Meal Requirements) – Subject consumed less than 75% of Period I, Day 1 dinner Study Hour 10.25	01	24
Other (Meal Requirements) – Subject consumed less than 75% of Period II, dinner Study Hour 10.25	07, 24, 47, 51	09, 23, 37
Other (Meal Requirements) – Subject consumed less than 75% of Period II, Check-in dinner Study Hour -13.5	43	14, 24, 33
Other (Sample Collection) – No sample collected at the Period I, study hour 6.00 blood draw	N/A	19
Other (Sample Collection) – No sample collected at the Period I, study hour 6.5 blood draw	50	N/A
Other (Sample Collection) – No sample collected at the Period I, study hour 7.00 blood draw	N/A	55
Other (Sample Collection) – No sample collected at the Period I, study hour 8.5 blood draw	N/A	55
Other (Sample Collection) – No sample collected at the Period I, study hour 11.00 blood draw	16	N/A
Other (Sample Collection) – No sample collected at the Period II, study hour 16.00 blood draw	55	N/A
Other (Vital Sign Collection) – Period I, study hour 24.00 vitals collected after the 24.00 hour blood draw	22, 34	10
Other (Vital Sign Collection) – Period II, study hour 24.00 vital signs collected greater than 10 minutes prior to the 24.00 hour blood sample collection	N/A	04

Comments on Adverse Events/Protocol Deviations:

- **Dropouts and Adverse Events:** Subject 1 (Period I) who received test, experienced vomiting twice at 10.5 and 11 hours. The firm stated that the severity of the condition was moderate and the effect was observed before 2X median of Tmax. So the firm dropped subject 1 prior to period II check in. The reviewer agrees with the firm for excluding subject 1.

- **Protocol Deviations:** There were some blood sampling deviations during fasting bioequivalence study. However, these sampling time deviations are minor deviations which occurred in less than 10% of the nominal time points, thus are considered to be insignificant. The firm used actual sampling times for its PK calculation.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Bioequivalence Study No. BUDE-0802 Budesonide										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.1	0.2	0.3	0.4	0.5	1.0	1.5	3.0	4.5	5.0
Inter day Precision (%CV)	1.60	2.75	2.65	2.79	2.34	2.01	2.20	1.92	2.41	1.97
Inter day Accuracy (%Actual)	101.50	98.90	99.40	98.50	97.68	99.73	100.27	101.70	101.67	100.68
Linearity	0.9955 - 0.9998									
Linearity Range (ng/mL)	0.1 ng/ml – 5.0 ng/ml									
Sensitivity/LOQ (ng/mL)	0.1 ng/ml									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.3	1.0	4.0	4.0 diluted
Inter day Precision (%CV)	25.90 (3.75)*	2.52	2.47	0.72
Inter day Accuracy (%Actual)	101.83 (99.52)*	100.20	97.99	97.85

*%CV and % Actual with a single outlier low QC dropped.

Comments on Study Assay Validation:

The QC samples in duplicate at three concentrations were incorporated in each assay run. The precision around the mean value was less than 20% of the CV for the two concentrations (1.0 ng/mL and 4.0 ng/mL) of QC samples. However the mean value deviated by more than ± 20% of the theoretical value for the QC sample of concentration 0.3 ng/mL.

In run 24, one value for the QC sample of concentration 0.3 ng/mL was greater than 15% of the nominal value (see table below for details).

Table 3
Analytical Performance of BUDE Quality Control Samples in Human Plasma
(Study BUDE0802)

Run Date	Curve Number	Low (0.3000 ng/mL) Dilution=1	%Error	Mid (1.000 ng/mL) Dilution=1	%Error	High (4.000 ng/mL) Dilution=2	%Error	High (4.000 ng/mL) Dilution=1	%Error
31-Jan-2008	5	0.2822	-5.93	0.9852	-1.48	NA		3.632	-9.20
		0.2935	-2.17	0.9726	-2.74	NA		3.698	-7.55
31-Jan-2008	6	0.2853	-4.90	1.001	0.10	NA		3.960	-1.00
		0.3014	0.47	0.9690	-3.10	NA		3.846	-3.85
31-Jan-2008	7	0.2893	-3.57	1.007	0.70	NA		3.855	-3.63
		0.2878	-4.07	0.9798	-2.02	NA		3.764	-5.90
31-Jan-2008	8	0.2839	-5.37	1.002	0.20	NA		3.984	-0.40
		0.2960	-1.33	1.002	0.20	NA		3.918	-2.05
31-Jan-2008	9	0.2993	-0.23	1.070	7.00	NA		3.933	-1.68
		0.2846	-5.13	0.9842	-1.58	NA		3.876	-3.10
01-Feb-2008	10	0.3013	0.43	0.9895	-1.05	NA		4.050	1.25
		0.2916	-2.80	1.012	1.20	NA		3.912	-2.20
01-Feb-2008	12	0.2943	-1.90	0.9777	-2.23	NA		3.921	-1.98
		0.2987	-0.43	0.9778	-2.22	NA		3.751	-6.23
01-Feb-2008	13	0.2918	-2.73	1.026	2.60	NA		4.063	1.58
		0.2903	-3.23	0.9813	-1.87	NA		3.895	-2.63
01-Feb-2008	14	0.3075	2.50	1.015	1.50	NA		3.924	-1.90
		0.3033	1.10	1.017	1.70	NA		3.945	-1.38
01-Feb-2008	15	0.2881	-3.97	1.012	1.20	NA		3.868	-3.30
		0.2873	-4.23	0.9858	-1.42	NA		4.005	0.13
01-Feb-2008	18	0.3010	0.33	1.004	0.40	NA		3.855	-3.63
		0.2972	0.93	0.9955	-0.45	NA		3.770	-5.75
02-Feb-2008	19	0.2983	-0.57	0.9929	-0.71	NA		4.013	0.33
		0.2847	-5.10	1.012	1.20	NA		3.750	-6.25
04-Feb-2008	20	0.2948	-1.73	0.9993	-0.07	NA		3.749	-6.28
		0.2910	-3.00	0.9889	-1.11	NA		3.984	-0.40
04-Feb-2008	21	0.3058	1.93	0.9981	-0.19	NA		3.914	-2.15
		0.3137	4.57	0.9746	-2.54	NA		3.809	-4.78
04-Feb-2008	22	0.2875	-4.17	0.9767	-2.33	NA		3.933	-1.68
		0.2979	-0.70	0.9622	-3.78	NA		3.746	-6.35
04-Feb-2008	23	0.3090	3.00	0.9836	-1.64	NA		3.858	-3.55
		0.2932	-2.27	0.9962	-0.38	NA		3.967	-0.83
04-Feb-2008	24	0.2923	-2.57	0.9653	-3.47	NA		3.852	-3.70
		~1.178*	292.67*	0.9596	-4.04	NA		3.844	-3.90
04-Feb-2008	25	0.2965	-1.17	1.019	1.90	NA		3.938	-1.55
		0.3020	0.67	0.9952	-0.48	NA		3.829	-4.28
04-Feb-2008	28	0.2944	-1.87	0.9509	-4.91	NA		3.728	-6.80
		0.2812	-6.27	0.9686	-3.14	NA		3.799	-5.03
04-Feb-2008	29	0.3037	1.23	0.9806	-1.94	NA		3.808	-4.80
		0.2940	-2.00	0.9581	-4.19	NA		3.764	-5.90
05-Feb-2008	26	0.2922	-2.60	0.9781	-2.19	NA		3.884	-2.90
		0.3056	1.87	0.9876	-1.24	NA		3.859	-3.53
05-Feb-2008	27	0.3001	0.03	0.9897	-1.03	NA		3.944	-1.40
		0.3191	6.37	1.019	1.90	NA		3.946	-1.35
05-Feb-2008	30	0.3004	0.13	1.016	1.60	NA		3.931	-1.73
		0.3055	1.83	1.025	2.50	NA		3.958	-1.05
05-Feb-2008	31	0.2961	-1.30	1.001	0.10	NA		3.873	-3.18
		0.2911	-2.97	0.9787	-2.13	NA		3.921	-1.98

By excluding that abnormal value, the precision around the mean value is less than 20% of the CV for QC concentration of 0.3 ng/mL.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

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

SOP No.	Effective Date of SOP	SOP Title
D-400-08	05/22/07	Reassay or Reinjection of Clinical Samples
D-416-05	10/19/06	Reassay of Whole Subjects

Table 28. Additional Comments on Repeat Assays

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

Summary/Conclusions, Study Assays:

Acceptable.

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Pending the firm's submission of PK parameters and statistical report.

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

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. BUDE-0802				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng *hr/mL)	9.89	10.19	0.97	91.6-102.8
AUC∞ (ng *hr/mL)	11.42	11.82	1.00	94.5-105.1
Cmax (ng/mL)	1.41	1.53	0.92	84.4-101.4

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

Pending the firm's submission of PK parameters and statistical report.

Table 32. Additional Study Information

Pending the firm's submission of PK parameters and statistical report.

Comments on Pharmacokinetic and Statistical Analysis:

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax, **provided by the firm**, met the criteria for BE.
- The firm did not submit the individual pharmacokinetic parameters for budesonide of all the subjects. In addition the firm also did not submit the linear and semi-log plots of the mean budesonide concentrations over time for both the treatments.
- The firm did not submit the statistical report of the fasting study.
- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax will be calculated by the reviewer after the firm submits the responses to the deficiency comments.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study:

Incomplete.

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

Pending the firm's submission of PK parameters and statistical report.

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

Pending the firm's submission of PK parameters and statistical report.

4.2 Formulation Data

Ingredient	Amount (mg) / Capsule	Amount (%) / Capsule	Functional category
Budesonide	3.0	1.41	Active
Ethylcellulose (b) (4)	(b) (4)		
Acetyltributyl Citrate, NF			
Polysorbate 80, NF (b) (4)			
Lactose Monohydrate, NF (b) (4)			
Crospovidone, NF (b) (4)			
Magnesium Stearate/Sodium Lauryl Sulfate (b) (4) (b) (4)			
Colloidal Silicon Dioxide, NF (b) (4)			
Methacrylic Acid Copolymer (b) (4)			
Talc, USP (b) (4)			
Triethyl Citrate, NF			
Sodium Hydroxide, NF			
(b) (4)			
Total Capsule Fill Weight	**212.4**	**100**	

(b) (4)

Following this page, 1 page withheld in full (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
Comments on the drug product formulation:	1. The amounts of all inactive ingredients in the formulation, calculated based on MDD, are below those used in the approved drug products based on CDER's Inactive Ingredient Guide (IIG) for Approved Drug Products. 2. The formulation is acceptable.

4.3 Dissolution Data

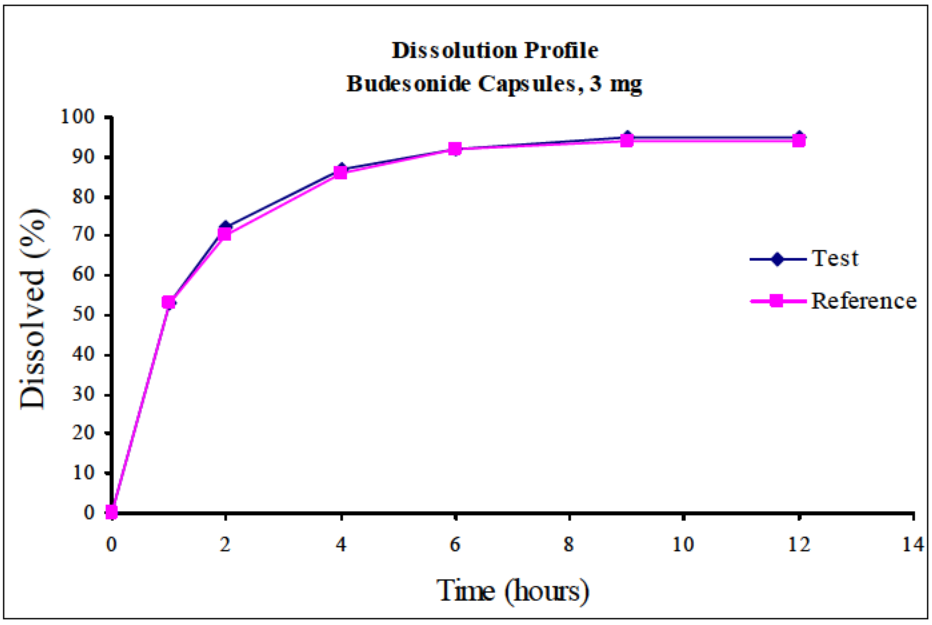
Dissolution Review Path	DARRTS: Dissolution review of ANDA 90410

Table 34. Dissolution Data

Dissolution Conditions	Apparatus:	2 (paddles)
	Speed of Rotation:	100 rpm
	Medium:	0.1 N HCl (Acid Stage), pH 6.8 Phosphate Buffer (Buffer Stage)
	Volume:	500 mL (Acid Stage), 500 mL (Buffer Stage)
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	Acid Stage: NMT (b) (4) in 2 hours Buffer Stage : (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) in 9 hours	
Dissolution Testing Site (Name, Address)	Mylan Pharmaceuticals Inc., Chemistry Research and Development Laboratories, 3711 Collins Ferry Road, Morgantown, WV, 26505	

Study Ref. No.	**Testing Date**	**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**
						Acid Stage	**Buffer Stage**						
						2 hours	**1 hour**	**2 hours**	**4 hours**	**6 hours**	**9 hours**	**12 hours**	
N/A	10/31/07	Budesonide Capsules Lot 1000093 Manufacture Date – 08/07/07	3 mg Capsules	12	Mean	0%	53%	72%	87%	92%	95%	95%	3.2.P.5.4 Batch Analysis
					Range	(b) (4)							
					%CV	0.0%	10.6%	8.3%	4.8%	3.0%	2.9%	2.7%	
N/A	11/02/07	Entocort® EC Capsules Lot MP0078 Expiration Date – 08/09	3 mg Capsules	12	Mean	0%	53%	70%	86%	92%	94%	94%	
					Range	(b) (4)							
					%CV	0.0%	9.8%	7.4%	3.2%	1.4%	1.4%	1.6%	

Figure 3. Dissolution Profiles



4.4 SAS Output

4.4.1 Fasting Study Data

None

4.4.2 Fasting Study Output

None

4.4.3 Fed Study Data

None

4.4.4 Fed Study Output

None

BIOEQUIVALENCE DEFICIENCIES

ANDA: 90-410

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Budesonide Capsules, 3 mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet.

The following deficiencies have been identified:

1. You did not specify the salt form of the anticoagulant EDTA used in the pre-study validation and during-study validation (i.e., K2EDTA, K3EDTA or NaEDTA). Please confirm whether the anticoagulant K2EDTA was used to prepare standard, quality control and stability samples of the pre-study method validation as well as the standard and quality controls of the during-study method validation. Per your study report, the subject plasma samples were collected in this anticoagulant K2EDTA.

2. Please submit the individual pharmacokinetic parameters of budesonide for all the subjects in both fasting and fed bioequivalence (BE) studies. In addition, please submit the individual and mean linear and semi-log plots of budesonide concentrations over time for both test and reference treatments of both fasting and fed BE studies.

3. Please submit the statistical report of both the fasting and fed BE studies.

4. In the Table 6 of the bioanalytical report (Module 5.3.1.4) you stated that plasma samples of the Subject 4 were not received by the analytical site. However, your SAS data file contains the budesonide concentrations at all time points in both the periods for Subject 4. In the meantime, the plasma concentrations of budesonide for subject 10 were missing from both the periods. Please clarify the discrepancies observed in the SAS dataset for the missing subject samples.

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

4.5 Outcome Page

ANDA: 90410

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
8848	3/13/2008	Bioequivalence Study	Fasting Study	1	1
8848	3/13/2008	Bioequivalence Study	Fed Study	1	1
				Bean Total:	2

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

/s/

SUMAN DANDAMUDI
08/11/2009

BING V LI
08/12/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/12/2009

DIVISION OF BIOEQUIVALENCE REVIEW OF AN AMENDMENT

ANDA No.	090410		
Drug Product Name	Budesonide Capsules		
Strength(s)	3 mg		
Applicant Name	Mylan pharmaceuticals, Inc.		
Address	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310		
Applicant's Point of Contact	S. Wayne Talton		
Contact's Telephone Number	304-599-2595		
Contact's Fax Number	304-285-6407		
Original Submission Date(s)	March 13, 2008 October 15, 2008 (Dissolution Acknowledgement)		
Submission Date(s) of Amendment(s) Under Review	August 21, 2009		
Reviewer	Suman Dandamudi		
OVERALL REVIEW RESULT	**ADEQUATE**		
DSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**DISSOLUTION**	**3 MG**	**ADEQUATE**
1	**FASTING STUDY**	**3 MG**	**ADEQUATE**
1	**FED STUDY**	**3 MG**	**ADEQUATE**

I. Executive Summary

Mylan Pharmaceuticals submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in the letter of August 21, 2009. In the original application, the firm submitted the results of fasting and fed BE studies comparing the test product, Budesonide, 3 mg, to the corresponding reference product, AstraZeneca, ENTOCORT EC® (Budesonide) Capsules, 3 mg. However, there were some deficiencies related to the clinical and analytical parts of the study. In the current application, the firm submitted acceptable responses to the deficiency comments made by DBE.

Each of the BE studies was designed as a single-dose, two-way crossover study in healthy subjects. The firm's fasting and fed BE studies are **acceptable**. The results are summarized in the tables below.

Budesonide, 3 mg Fasting Bioequivalence Study No. BUDE-0722, N= 54 (Male=23 and Female=31) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	8.31	7.73	1.08	101.04	114.40
AUC∞ (ng·hr/mL)#	10.04	9.60	1.05	98.74	110.69
Cmax (ng/mL)	1.13	1.04	1.08	99.04	117.33

#N=44

Budesonide, 3 mg Fed Bioequivalence Study No. BUDE-0802, N= 62 (Male=32 and Female=30) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng·hr/mL)	9.89	10.19	0.97	91.59	102.81
AUC∞ (ng·hr/mL)#	11.19	11.36	0.99	93.25	104.12
Cmax (ng/mL)	1.41	1.53	0.92	84.38	101.36

N= 56

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is **acceptable** with no deficiencies.

II. Table of Contents

III. Background

1. The firm submitted its original application on March 13, 2008. DBE had done a "dissolution only" review on this ANDA (DARRTS: dissolution review of ANDA 090410). The firm conducted its dissolution testing using its own proposed dissolution method:

Medium:	Acid stage: 0.1 N HCl Buffer stage: pH 6.8 Phosphate Buffer
Volume	500 mL for acid stage and 500 mL for buffer stage
Apparatus:	USP apparatus II (Paddle)
Speed:	100 RPM

This is acceptable since the firm conducted the study prior to the FDA-recommended dissolution method being posted in the FDA website. The firm's initially proposed specification of "Acid Stage: NMT (b) (4) in 2 hours, Buffer Stage: (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) in 9 hours" was not acceptable. DBE recommended the firm to acknowledge the FDA-recommended specification of "Acid Stage: NMT (b) (4) in 2 hours, Buffer Stage: (b) (4) in 1 hour, (b) (4) in 2 hours, NLT (b) (4) n 6 hours". In its amendment dated on 10/15/2008, the firm acknowledged the FDA-recommended dissolution specification. The dissolution testing is acceptable.

2. The firm, in its original application, also submitted the fasting and fed bioequivalence studies comparing its Budesonide Capsules, 3 mg, to the AstraZeneca's ENTOCORT EC® (Budesonide) Capsules, 3 mg. The BE studies

were found incomplete (DARRTS: Bioequivalence review of ANDA 90410) due to deficiencies related to the clinical and analytical part of the studies.

3. In the current amendment, the firm submitted its responses to the deficiency comments made by DBE. The firm confirmed the K2EDTA was used for the pre-study method validation. The firm also clarified the missing samples of subjects 4 and 10 of the fasting BE study.

IV. Submission Summary

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

See the review of the original submission DARRTS: Bioequivalence review of ANDA 090410.

B. Contents of Submission

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

C. Review of Submission

Deficiency 1: *You did not specify the salt form of the anticoagulant EDTA used in the pre-study validation and during-study validation (i.e., K2EDTA, K3EDTA or NaEDTA). Please confirm whether the anticoagulant K2EDTA was used to prepare standard, quality control and stability samples of the pre-study method validation as well as the standard and quality controls of the during-study method validation. For your study report, the subject plasma samples were collected in this anticoagulant K2EDTA.*

Firm's Response to Deficiency 1: K_2EDTA plasma was used throughout method validation and the BUDE-0722 and BUDE-0802 studies for the preparation of all plasma samples, including calibration standards, quality control (QC) samples, and stability samples. Prior to use in the validation or studies, K_2EDTA plasma (obtained from multiple

individual donors) was combined into composite pools. The plasma composite pools used during method validation and both studies, as well as the individual plasma sources used to prepare each composite are summarized in Table 1. Additionally, copies of the source documents for the preparation of these plasma composites and pages from the laboratory's Blank Matrix Receipt logbooks, used to track the individual plasma sources from which these composites were prepared, are provided Section 5.4, References.

Reviewer's Comments on Firm's Response: The firm's response is acceptable. The firm used K_2EDTA as anticoagulant in their fasting and fed BE studies. So they conducted pre-study and with-in study validation using plasma containing K_2EDTA as the matrix.

Deficiency 2: *Please submit the individual pharmacokinetic parameters of budesonide for all the subjects in both fasting and fed bioequivalence (BE) studies. In addition, please submit the individual and mean linear and semi-log plots of budesonide concentrations over time for both test and reference treatments of both fasting and fed BE studies.*

Firm's Response to Deficiency 2: As noted in our response to FDA Comment 4, all samples released for assay were utilized in the Pharmacokinetic Study Report. As there were no errors in reporting the data, the Pharmacokinetic Study Report is not affected. The individual pharmacokinetic parameters are located in Appendix 16.1.1.2 of the Pharmacokinetic Study Report provided in Section 5.3.1.2 of the original ANDA for respective studies BUDE-0722 and BUDE-0802. Individual and mean linear and semi-log plots are located in Appendix 16.1.1.5 for respective studies BUDE-0722 and BUDE-0802.

Reviewer's Comments on Firm's Response: The firm's response is acceptable.

Deficiency 3: *Please submit the statistical report of both the fasting and fed BE studies.*

Firm's Response to Deficiency 3: As noted in our response to FDA Comment 4, all samples released for assay were utilized in the Pharmacokinetic Study Report. As there were no errors in reporting the data, the Pharmacokinetic Study Report is not affected. Statistical Analyses may be found in Appendices 16.1.2.1 and 16.1.2.2 of the Pharmacokinetic Report provided in Section 5.3.1.2 of the original ANDA for respective studies BUDE-0722 and BUDE-0802.

Reviewer's Comments on Firm's Response: The firm's response is acceptable.

Deficiency 4: *In the Table 6 of the bioanalytical report (Module 5.3.1.4) you stated that plasma samples of the Subject 4 were not received by the analytical site. However, your SAS data file contains the budesonide concentrations at all time points in both the periods for Subject 4. In the meantime, the plasma concentrations for budesonide for subject 10 were missing from both the periods. Please clarify the discrepancies observed in the SAS dataset for the missing subject samples.*

Firm's Response to Deficiency 4: Only a single sample from BUDE-0722 (Subject 4, the period 2 - 14 h sample), was not received from the clinical site. All the other samples from this subject were analyzed and therefore had reportable concentration values. Table 6 of the BUDE-0722 bioanalytical report correctly listed this single sample from Subject 4 as not having been received. Accordingly, Table 4 of the report correctly showed a null value for this sample, and determined concentrations for the other samples from this subject. Likewise, the SAS dataset from BUDE-0722 correctly showed only a single missing value (period 2 - 14 h) for Subject 4. Please refer to Tables 4 and 6 from the BUDE-0722 Bioanalytical Report, as well as the SAS dataset from this study, in Section 5.3.1.4 of the original ANDA.

As described in the BUDE-0722 Pharmacokinetics Study Report, Subject 10 was missing several samples around expected time of peak drug concentration (in Period 2) and for this reason the subject was discontinued from the study by Mylan prior to bioanalysis, as documented per the Notification to the Bioanalytical Department of Subjects Discontinued from Study provided in Section 5.4, References.

Reviewer's Comments on Firm's Response: The firm's response is acceptable.

D. Deficiency Comments

None.

E. Recommendations

1. The Division of Bioequivalence accepts the fasting BE study No. BUDE-0722 conducted by the Mylan Pharmaceuticals, Inc on its Budesonide Capsules, 3 mg, lot # 1000093, comparing it to AstraZeneca's ENTOCORT EC® (Budesonide) Capsules, 3 mg, lot # MP0078.

2. The Division of Bioequivalence accepts the fed BE study No. BUDE-0802 conducted by the Mylan Pharmaceuticals, Inc on its Budesonide Capsules, 3 mg, lot # 1000093, comparing it to AstraZeneca's ENTOCORT EC® (Budesonide) Capsules, 3 mg, lot # MP0078.

3. The firm's *in vitro* dissolution testing is acceptable. The dissolution testing should be conducted using the following method:

Apparatus:	USP Apparatus 2 (paddle)
Medium:	Acid stage: 0.1 N HCl
	Buffer stage: pH 6.8 Phosphate Buffer
Volume:	500 mL for acid stage and 500 mL for buffer stage

Specifications: Acid stage: NMT (b) (4) of labeled content after 2 hrs.
Buffer stage: 1 hour (b) (4) of labeled content
2 hours (b) (4) of labeled content
6 hours NLT (b) (4) of the labeled content

F. Pharmacokinetic Results

A. Fasting Study Data

Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Fasting Bioequivalence Study, Study No. BUDE-0722									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/mL)	10.128	69.30	1.98	34.80	9.506	69.12	1.75	33.78	1.07
AUC∞ (hr *ng/mL)	11.979	66.16	3.38	39.94	11.425	65.21	2.67	37.55	1.05
Cmax (ng/mL)	1.381	72.47	0.37	4.86	1.270	70.56	0.34	4.70	1.09
Tmax* (hr)	4.500	.	1.50	10.00	4.500	.	2.00	6.50	1.00
Kel (hr^{-1})	0.145	24.92	0.08	0.23	0.134	26.36	0.06	0.21	1.09
T1/2 (hr)	5.080	24.94	3.07	8.68	5.611	31.23	3.37	11.45	0.91

Geometric Means and 90% Confidence Intervals - Firm Calculated

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. BUDE-0722				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (ng *hr/mL)	8.27	7.72	1.08	101.0-114.4
AUC∞ (ng *hr/mL)	9.57	9.04	1.06	100.4-112.2
Cmax (ng/mL)	1.12	1.04	1.08	99.0-117.3

Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. BUDE-0722					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/mL)	8.31	7.73	1.08	101.04	114.40
AUC∞ (hr *ng/mL)#	10.04	9.60	1.05	98.74	110.69
Cmax (ng/mL)	1.13	1.04	1.08	99.04	117.33

#N=44

Note: All the pharmacokinetic parameters calculated by the reviewer in the verification of study were done using the SAS code "calcke".

Additional Study Information

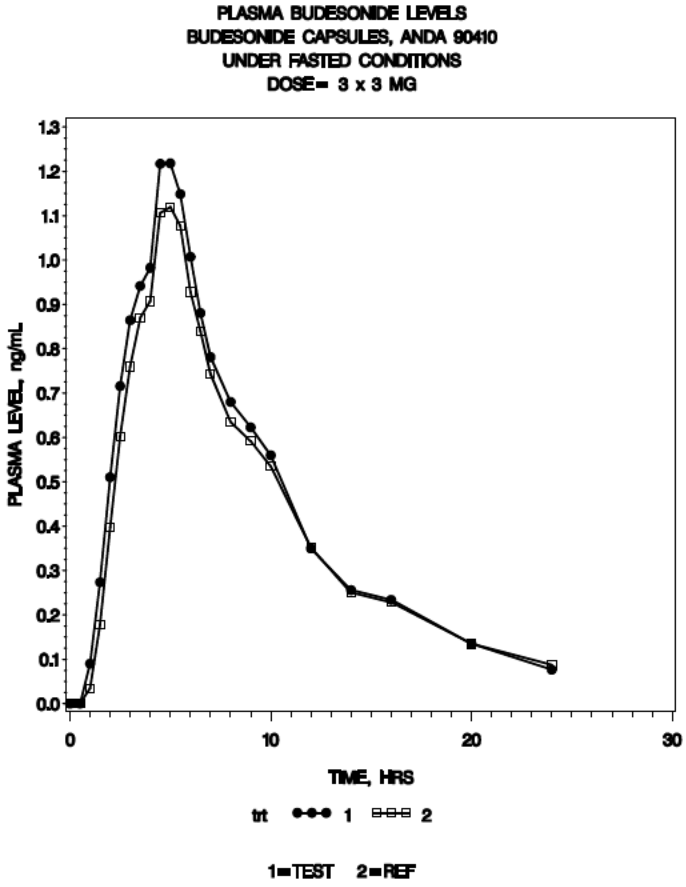
Root mean square error, AUC0-t	0.1926	
Root mean square error, AUC∞	0.1592	
Root mean square error, Cmax	0.2627	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	44 (Reviewer) 52 (Firm)	44 (Reviewer) 54 (Firm)
Do you agree or disagree with firm's decision?	No	No
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	44	0.89	0.77	0.97
Reference	44	0.88	0.76	0.96

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

	Test (n=54)		Reference (n=54)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	0.00	.	0.00	.	.
1.00	0.09	174.44	0.03	211.57	2.60
1.50	0.27	124.02	0.18	119.71	1.54
2.00	0.51	95.87	0.40	98.60	1.28
2.50	0.72	85.49	0.60	81.78	1.19
3.00	0.86	83.23	0.76	74.58	1.14
3.50	0.94	79.92	0.87	76.01	1.08
4.00	0.98	71.43	0.91	78.79	1.08
4.50	1.22	69.07	1.11	73.01	1.10
5.00	1.22	77.06	1.12	79.01	1.09
5.50	1.15	78.67	1.08	78.54	1.07
6.00	1.01	77.63	0.93	75.30	1.09
6.50	0.88	72.88	0.84	75.64	1.05
7.00	0.78	72.21	0.74	70.71	1.05
8.00	0.68	70.33	0.63	70.50	1.07
9.00	0.62	73.28	0.59	70.04	1.05
10.00	0.56	69.77	0.54	70.98	1.05
12.00	0.35	70.24	0.35	70.64	1.00
14.00	0.26	78.15	0.25	82.17	1.02
16.00	0.23	81.16	0.23	81.48	1.02
20.00	0.13	103.32	0.13	108.06	1.00
24.00	0.08	144.61	0.09	128.60	0.88

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



B. Fed Study Data

Arithmetic Mean Pharmacokinetic Parameters- Reviewer Calculated

Fed Bioequivalence Study, Study No. BUDE-0802									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-t (hr *ng/mL)	11.290	56.91	2.65	37.57	11.661	55.64	3.45	32.27	0.97
AUC∞ (hr *ng/mL)	12.814	57.57	3.00	42.48	12.956	56.53	4.19	35.18	0.99
Cmax (ng/mL)	1.663	60.25	0.36	4.73	1.785	62.77	0.44	5.52	0.93
Tmax* (hr)	6.500	.	4.00	24.00	6.500	.	4.00	24.00	1.00
Kel (hr^{-1})	0.127	29.70	0.07	0.35	0.135	24.31	0.08	0.30	0.94
T1/2 (hr)	5.777	23.33	1.97	10.47	5.355	20.26	2.28	8.42	1.08

Geometric Means and 90% Confidence Intervals - Firm Calculated

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study No. BUDE-0802				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC0-t (ng *hr/mL)	9.89	10.19	0.97	91.6-102.8
AUC∞ (ng *hr/mL)	11.42	11.82	1.00	94.5-105.1
Cmax (ng/mL)	1.41	1.53	0.92	84.4-101.4

Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Budesonide 3 × 3 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fed Bioequivalence Study, Study No. BUDE-0802					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/mL)	9.89	10.19	0.97	91.59	102.81
AUC∞ (hr *ng/mL)#	11.19	11.36	0.99	93.25	104.12
Cmax (ng/mL)	1.41	1.53	0.92	84.38	101.36

N= 56

Note: All the pharmacokinetic parameters calculated by the reviewer in the verification of study were done using the SAS code "calcke".

Additional Study Information

Root mean square error, AUC0-t	0.1925	
Root mean square error, AUC∞	0.1742	
Root mean square error, Cmax	0.3056	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	56 (Reviewer) 57 (Firm)	56 (Reviewer) 61 (Firm)
Do you agree or disagree with firm's decision?	No	No
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	56	0.88	0.78	0.95
Reference	56	0.89	0.75	0.96

Comments on Pharmacokinetic and Statistical Analysis:

Fasting Study:

- The firm excluded subjects 15 and 31 who received test formulation for the calculation of Kel and AUCi since the ratio of AUC0-t/AUC∞ ratio < 0.8. The reviewer agrees with the firm for excluding the above subjects from Kel and AUCi analysis after checking their data. The reviewer also excluded the above mentioned subjects from Kel and AUCi analysis. In addition the reviewer also excluded subjects 6, 9, 17, 20, 30, 42, 44, 47 who received test formulation and reference formulations for the calculation of Kel and AUCi since the ratio of AUC0-t/AUC∞ ratio < 0.8.

Fed Study:

- The adverse event (emesis) was observed at 10.5 hours and 11 hours for subject 1, which is before 2X median of Tmax, so the subject 1 need to be excluded from the study. The reviewer agrees with the firm for excluding subject 1 from the study.

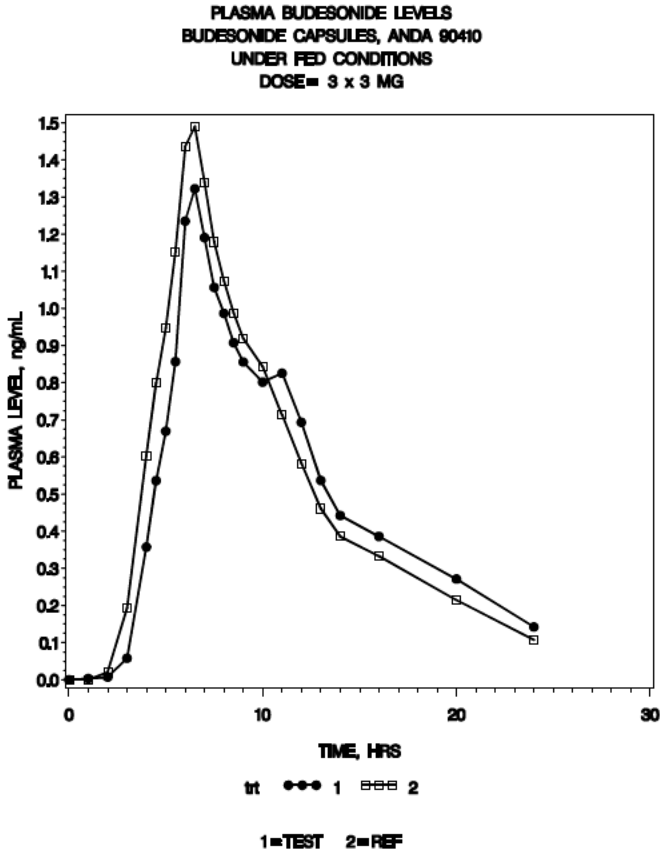
- The firm excluded subjects 35, 37, 39, 47, 52 who received test formulation and subject 37 who received reference formulation for the calculation of Kel and AUCi since the ratio of AUC0-t/AUC∞ ratio < 0.8. The reviewer agrees with the firm for excluding the above subjects from Kel and AUCi analysis after checking their data. The reviewer also excluded the above mentioned subjects from Kel and AUCi analysis. In addition the reviewer also excluded subject 63 who received test formulation and subjects 35, 39, 47, 52 who received reference formulations for the calculation of Kel and AUCi since the ratio of AUC0-t/AUC∞ ratio < 0.8.

- The 90% CI's for the least squares geometric means of Ln AUC0-t, Ln AUC∞ and LnCmax, calculated by both the reviewer and the firm met the criteria for BE for both fasted and fed BE studies.

Table 22. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=62)		Reference (n=62)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	0.00	787.40	0.00	.	.
2.00	0.01	610.54	0.02	293.45	0.36
3.00	0.06	224.88	0.19	321.56	0.30
4.00	0.36	151.68	0.60	136.85	0.59
4.50	0.54	128.85	0.80	111.48	0.67
5.00	0.67	109.72	0.95	99.05	0.71
5.50	0.86	97.63	1.15	85.19	0.74
6.00	1.24	82.91	1.44	72.96	0.86
6.50	1.32	76.00	1.49	68.03	0.89
7.00	1.19	71.79	1.34	67.34	0.89
7.50	1.06	65.45	1.18	60.43	0.90
8.00	0.99	61.66	1.07	55.17	0.92
8.50	0.91	55.79	0.99	51.93	0.92
9.00	0.86	53.03	0.92	49.69	0.93
10.00	0.80	50.51	0.84	49.95	0.95
11.00	0.83	77.26	0.71	55.85	1.16
12.00	0.69	74.75	0.58	59.01	1.19
13.00	0.54	69.81	0.46	56.69	1.17
14.00	0.44	62.26	0.39	56.37	1.15
16.00	0.39	68.55	0.33	62.61	1.16
20.00	0.27	71.57	0.21	79.99	1.26
24.00	0.14	111.73	0.11	146.61	1.32

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



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BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090410

APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Budesonide Capsules, 3 mg

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page and has no further question at this time.

We acknowledge that you will conduct dissolution testing using the following dissolution method and specifications:

The dissolution testing should be conducted in 500 mL of acid stage (0.1 N HCl) and 500 mL of buffer stage (pH 6.8 Phosphate Buffer) at 37°C ± 0.5°C using USP apparatus II (Paddle) at 100 rpm. The test product should meet the following specifications:

Acid stage:

2 hours: NMT (b) (4) of labeled amount of budesonide.

Buffer stage:

1 hour: (b) (4) of labeled amount of budesonide

2 hours: (b) (4) of labeled amount of budesonide

6 hours: NLT (b) (4) of the labeled amount of budesonide

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
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. Outcome Page

ANDA: 090410

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
9417	8/21/2009	Other	Study Amendment	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/

SUMAN DANDAMUDI
10/23/2009

BING V LI
10/24/2009

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/27/2009