CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211929Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **January 25, 2019**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 211929**

Subject: Final Recommendation for NDA 211929

At the time when the CMC Review #1 was completed on December 4, 2018 it had noted the following pending issues:

- The label/labeling issues were not resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised immediate container labels and Prescribing Information (PI) on January 25, 2019 and the submitted CMC sections of the labeling/labels were reviewed and found acceptable. **(See the Attachment)**

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch V Division of New Drug Products II
January 25, 2019

Hitesh N. Shroff -S

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **Jan 25, 2019**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch V

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, ONDP/Division II/Branch V

To: **Labeling Review #1 of NDA 211929**

Subject: **Final labeling/labels**

The Labeling review #1 has noted the following pending issues:

A. Regarding PI

I. Highlights of Prescribing Information

- Budesonide (b) (4) should be revised to:
  Budesonide Extended-Release Capsules

II. Full Prescribing Information

For Section 2, "DOSAGE AND ADMINISTRATION"

- (b) (4) should be revised to:
  (b) (4)

For section 3, "DOSAGE FORM AND STRENGTH"

- The dosage form should be revised to:
  "Extended-Release Capsules"

For Section 11, "DESCRIPTION"

- The established name should be revised to:
  "Budesonide Extended-Release Capsules"
- Dose strength should be changed to read "each extended-release capsule …contains 6 mg or 9 mg…"

For Section 16, "HOW SUPPLIED/STORAGE AND HANDLING"

- Dosage form should be revised to (b) (4)
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:
Immediate Container label

- The proprietary name, established name, dosage form and strength should be revised as following:

  Budesonide Extended-Release Capsules

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

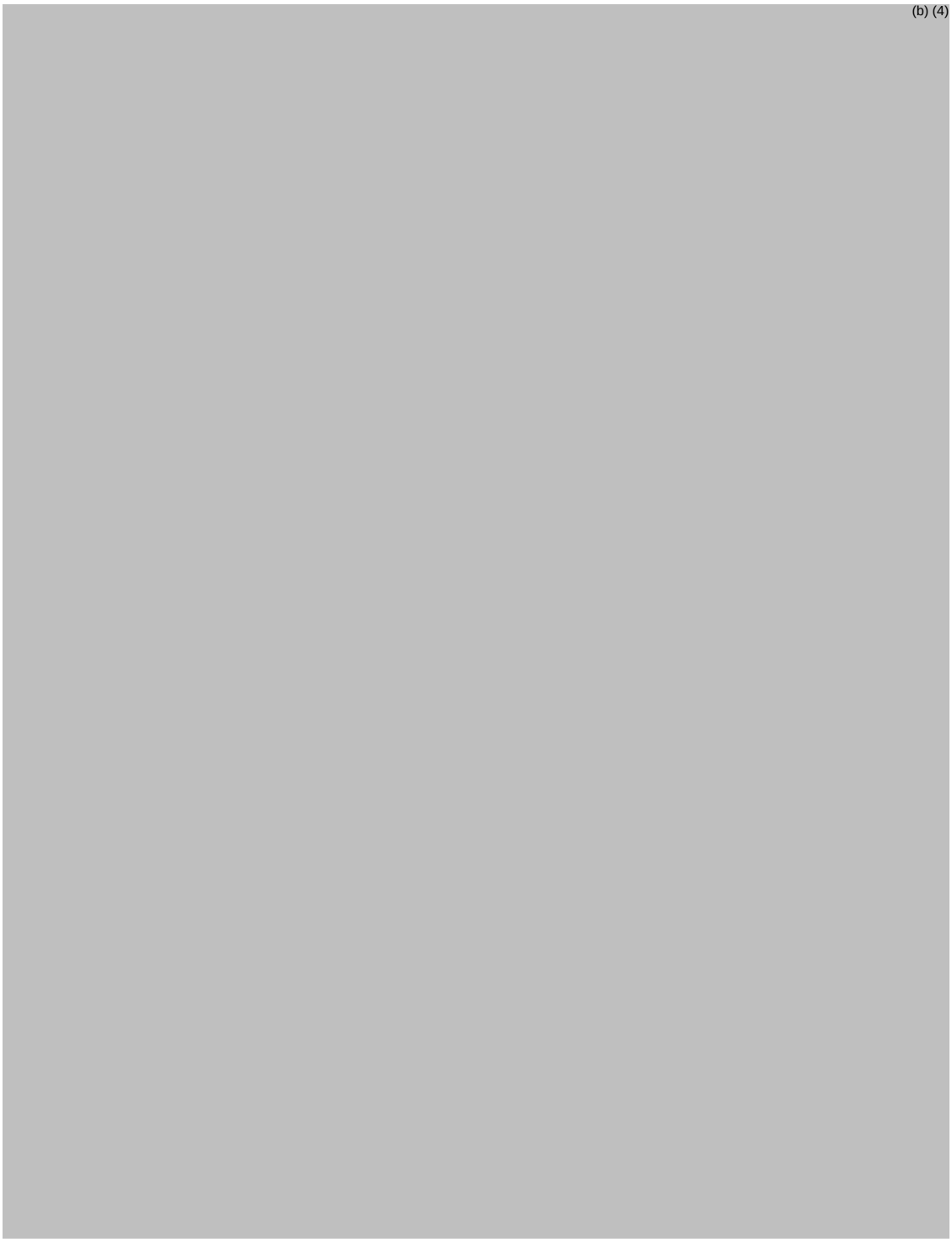
The above requests have been implemented in the revised labeling. A proprietary name Otikos has been adequately added in the labeling. The revised container labels are satisfactory and provided in the **Attachment**.

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

Attachment:

Immediate bottle labels for 6 mg and 9 mg in 30, 100 and 500 capsules are provided in the amendment. Information on the labels of 6 mg and 9 mg capsules is the same except differences in the dose strengths. The labels for the 6 mg capsules are shown below.



1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Zhengfang Ge

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Moo Jhong Rhee

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QUALITY ASSESSMENT

Recommendation: As of this review, this 505 (b)(2) NDA is *not* ready for Approval in its present form per 21 CFR 314.125(b)(6).

NDA 211929

OPQ Review #1

Drug Name/Dosage Form	Budesonide Extended-Release Capsules
Strength	6mg and 9 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharma Global FZE, Sharjah, U.A.E.
US agent, if applicable	Mr. Ronak Patel, Sun Pharmaceuticals, Inc.; Princeton, NJ

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	3/30/2018	OPQ
Amendment	8/6/2018	Biopharmaceutics and Drug Product
Amendment	9/18/2018	Biopharmaceutics
Amendment	9/28/2018	Drug Substance and Drug Product
Amendment	9/28/2018	Biopharmaceutics
Amendment	11/2/2018	Process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Labeling	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Sydney Choi	CDER/OPQ/OPF/ DPAIII/PABVIII
Biopharmaceutics	Hansong Chen	OMPT/CDER/OPQ/ONDP/DB/BBII
Microbiology	Sydney Choi	CDER/OPQ/OPF/ DPAIII/PABVIII
Facilities	Sydney Choi	CDER/OPQ/OPF/ DPAIII/PABVIII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Environmental Analysis (EA)	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	11	Dr. Ramsharan Mittal, October 11, 2017, adequate	LOA: March 30, 2018
	Type III			Active	Not reviewed, Information provided in NDA	LOA: June 6, 2012
	Type III			Active	Not reviewed, Information provided in NDA	LOA: May 4, 2009
	Type III			Active	Not reviewed, Information provided in NDA	LOA: June 5, 2009
	Type III			Active	Not reviewed, Information provided in NDA	LOA: June 15, 2009
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Oct 21, 2011
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Oct 21, 2011
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Jan 12, 2015
	Type III			Active	Not reviewed, Information provided in NDA	LOA: May 4, 2009
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Jan 5, 2015
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Oct 24, 2012
	Type III			Active	Not reviewed, Information provided in NDA	LOA: May 15, 2014
	Type III			Active	Not reviewed, Information provided in NDA	LOA: May 2, 2014
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Jan 4, 2010
	Type III			Active	Not reviewed, Information provided in NDA	LOA: Sept 9, 2013

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021324	ENTOCORT® EC (budesonide) capsules
PIND	116777	Budesonide Capsules, 6 mg and 9 mg (Sun Pharmaceuticals Industries, Ltd.)

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The Office of Process and Facilities (OPF) has made a final overall "Approval" recommendation for the facilities involved in this application.

The label/labeling issues have ***not*** been satisfactorily resolved as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per CFR 314.125(b)(6), until above mentioned issues are satisfactorily resolved. **(**see the **List of Deficiencies)**

II. Summary of Quality Assessments

A. Product Overview

Budesonide Extended-Release Capsule is an anti-inflammatory corticosteroid indicated for treatment of Crohn's disease.

The listed reference drug, Entocort EC (budesonide) capsules, 3 mg, was first approved in October 2001 (NDA 021324) from Perrigo Pharma International DAC, USA also for the same indication.

Sun Pharma Global did not conduct any clinical or nonclinical studies for Budesonide capsules relying on Agency's prior determination of safety and efficacy of budesonide given 9 mg/day for up to 8 weeks and at a dose of 6 mg/day for up to 3 months. The higher strength capsules are developed to reduce the number of Entocort EC capsules taken daily.

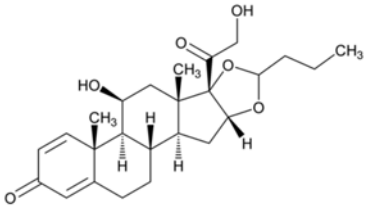
Proposed Indication(s) including Intended Patient Population	Budesonide extended-release capsule is indicated for: • Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older. • Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults.
Duration of Treatment	One 9 mg capsule per day up to 8 weeks. Can be repeated 8-week course for recurring episodes.
Maximum Daily Dose	9 mg per day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:
The active ingredient, budesonide, USP is a white to off-white, odorless, crystalline powder. It is practically insoluble in water and sparingly soluble in alcohol. It is a chiral compound. Its specific rotation is between +90° and 120° (b) (4) (b) (4) (b) (4)

Budesonide, USP is manufactured by Sun Pharmaceutical Industries Ltd.; India. The complete CMC information is provided in DMF (b) (4) from the manufacturer. A letter of authorization from the manufacturer was provided. The DMF was reviewed by Dr. Ramsharan Mittal on Oct 11, 2018 and was deemed adequate.

Budesonide is a mixture of two isomers Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-11,21-dihydroxy-, [11β,16α(*R*)], and 16α,17-[(*S*)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione; (2) (*RS*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Its empirical formula is $C_{25}H_{34}O_6$, with a molecular weight of 430.53. Its molecular structure is as follows:



The applicant has provided Certificate of Analysis (COA) of two batches of the drug substance used in the manufacture of three batches of 6 mg and 9 mg capsules.

The identity, purity and quality of the drug substance, Budesonide, is controlled by its specification which includes description, identification by infrared and UV spectroscopy, assay and impurities by HPLC; heavy metals, particle size distribution and bioburden. The drug substance specification is deemed adequate per drug substance reviewer, Dr. Ramsharan Mittal. (See **the Drug Substance** review)

Based on the long-term and accelerated stability data of three registration batches of budesonide provided in DMF (b) (4) a re-test period of (b) (4) was established when stored in a (b) (4) (b) (4)

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all drug substance manufacturing and testing facilities. (See the **Facilities** review)

The API are manufactured by Sun Pharmaceutical Industries Ltd.; India is

controlled to conform to the requirements (specification) to produce Budesonide extended-release capsules, 6 mg and 9 mg.

Drug Product:

Budesonide capsules are supplied as hard gelatin imprinted extended-release capsules. Each capsule contains 6 mg and 9 mg budesonide. The drug product includes a (b) (4) (b) (4) The budesonide pallets are encapsulated in hard gelatin capsules.

(b) (4)

The drug product is manufactured by Sun Pharmaceutical Industries Ltd., India. The manufacturing process consists of the following key manufacturing steps: (b) (4) (b) (4) (b) (4) The process selection, in-process controls, drug product release tests and executed batch records were satisfactory. The drug product manufacturing process and microbiology sections were reviewed and deemed acceptable. (See **Process** review)

The overall control strategy for the drug product's identity, strength, purity and quality deemed adequate based on raw material controls, drug product specification including description, identity, assay, impurities, dissolution, content uniformity, microbial limits, elemental impurities etc. The applicant developed and used non-compendial, validated in-house analytical methods. The (b) (4) was controlled per ICH Q3B.

The dissolution method development, dissolution data, dissolution acceptance criteria, biowaiver for the lower strength (i.e. 6 mg) and in vitro alcohol induced dose dumping were reviewed. The applicant has provided sufficient data to support the biowaiver of the lower strength (i.e. 6 mg) so the biowaiver for 6 mg strength is granted. The in vitro alcohol induce dose dumping study shows that alcohol can induce dose dumping of the proposed drug products.

Based on the long-term and accelerated stability data of the drug product assuring the identity, strength, purity and quality, a 24-month of expiration dating period when stored at 25ºC in the proposed container closure system is granted. (See the **Drug Product** review)

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for the drug product manufacturing and testing facilities. (See the **Facility** review)

The applicant requested categorical exclusion for environmental analysis on the basis that Budesonide capsules will be administered at the same dosage level, for the same indications as the listed drug. The applicant also certified that, it is following all federal, state and local environmental protection requirement. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31 was deemed acceptable. (See the **Drug Product** review)

The labels and labeling issues are ***not*** satisfactorily resolved from the CMC perspective per the labeling review. (See the **List of Deficiencies** below and **Labeling** review).

C. Lifecycle Management Consideration (NDA only)

None

D. Special Product Quality Labeling Recommendations (NDA only)

None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies:

The following labeling comments should be resolved with the applicant.

A. Regarding PI

I. Highlights of Prescribing Information

- Budesonide (b) (4) should be revised to:
  Budesonide extended-release capsules

II. Full Prescribing Information

For section 3, "DOSAGE FORM AND STRENGTH"

- The dosage form should be revised to:
  "extended-release capsules"

For section 11, "DESCRIPTION"

- The dosage form should be revised to:
  "extended-release capsules"

- Dose strength should be changed to read "each extended-release capsule …contains 6 mg or 9 mg…"

For Section 16, "HOW SUPPLIED/STORAGE AND HANDLING"

- Dosage form should be changed to (b) (4)
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:

Immediate Container label

- The proprietary name, established name, dosage form and strength should be revised as following:

Budesonide Extended-release Capsules

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
December 04, 2018

Hitesh N. Shroff -S

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BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA/ANDA: NDA 211929

Drug Product Name / Strength: Budesonide Capsules, 6 mg and 9 mg

Route of Administration: Oral

Applicant Name: Sun Pharma Global FZE

Review Recommendation: **Adequate**

Review Summary:

The Listed Drug Entocort® EC (budesonide) capsules, 3 mg, developed by (b) (4) was approved by the FDA under NDA 021324 on 10/02/2001. It is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, and the maintenance of clinical remission for up to 3 months.

(b) (4)

The same Applicant further developed Budesonide Capsules, 6 mg and 9 mg and submitted under NDA 211929 seeking approval through 505(b)(2) pathways.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution acceptance criterion, biowaiver for the lower strength (i.e., 6 mg), and in vitro alcohol induced dose dumping.

The proposed dissolution method was reviewed and found acceptable. However, the dissolution method does not have meaningful discriminatory power based on the *in vitro* study conducted. The initial dissolution acceptance criteria proposed by the Applicant were reviewed but found to be liberal. The following acceptance criteria proposed by the Agency were conveyed in an IR to the Applicant and accepted by the Applicant:
Acid stage:
2 hours: NMT (b) (4)%
Buffer stage:
2.5 hours: (b) (4)%

4 hours: (b) (4) %
8 hours NLT (b) (4) %

The Applicant provided sufficient data to support the biowaiver of the lower strength (i.e. 6 mg). The biowaiver for 6 mg strength is therefore, granted.
The in vitro alcohol induced dose dumpling study shows that alcohol can induce dose dumping of the proposed drug products. This finding has been conveyed to the Clinical Pharmacology team.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 211929 for Budesonide Capsules, 6 mg and 9 mg is **adequate,** therefore, recommended for approval.

List Submissions being reviewed (table):

3/30/2018	NDA 211929/Original submission
8/6/2018	eCTD-0007/Response to Biopharmaceutics Information Requests
9/28/2018	eCTD-0012/Response to Biopharmaceutics Information Requests

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: The Applicant claimed that Budesonide is a BCS Class II drug, which has low solubility and high permeability.

Solubility:

Table 1. Aqueous solubility data as a function of pH for Budesonide at 37°C±0.5°C

Sr. No.	Solution Details	Saturated Solubility at 37°C ± 0.5°C (mg/mL)	Dose Solubility Volume# (mL)
1	Buffer pH 1.2 (Hydrochloric acid buffer)	0.02321	387.764
2	Buffer pH 2.1 (Hydrochloric acid buffer)	0.02349	383.142
3	Buffer pH 3.0 (Citrate buffer)	0.08499	105.895
4	Buffer pH 4.5 (Acetate buffer)	0.02590	347.490
5	Buffer pH 6.8 (Phosphate buffer)	0.02292	392.670
6	Buffer pH 7.4 (Phosphate buffer)	0.02434	369.762

Permeability: The Applicant did not report the permeability of budesonide.

Dissolution: See Section "Dissolution Method and Acceptance Criteria".

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate}***

1. Dissolution method

The Applicant developed the following dissolution method for Budesonide Capsules, 6 mg and 9 mg:

Table 2. The proposed dissolution method

Apparatus	USP type II (paddle) with sinker (Size 1)
Speed	75 rpm
Dissolution media	Acid stage: 0.1 N hydrochloric acid Buffer stage: Phosphate buffer pH 6.0
Volume	Acid stage: 1000 mL; Buffer stage: 1000 mL
Time	Acid stage: 2.0 hrs. Buffer stage: 15 mins, 20 mins, 30 mins, 45mins, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours
Temperature	37 ± 0.5 °C
Proposed acceptance criteria	Acid stage: NMT (b) (4)% Buffer stage: 3 hours: (b) (4)% 6 hours: % 10 hours NLT (b) (4)%

(b) (4)

(b) (4)

[redacted]

Reviewer's Assessment: *{Adequate}*

Because the proposed product is a delayed release product, the Applicant conducted an in vitro alcohol dose dumping study in two different media: 0.1 N HCl and Phosphate buffer pH 6.0. The results are shown in Tables 10, 11, 12, and 13.

Table 10. Mean dissolution data of JKR4660 in 0.1 N HCl with alcohol

Batch Number/Time points (min)	15	30	45	60	75	90	105	120
9 mg Batch JKR4660 in 0.1 N HCl with 0% of alcohol	0	0	1	1	1	1	1	1
9 mg Batch JKR4660 in 0.1 N HCl with 5% of alcohol	0	0	1	1	1	1	2	2
9 mg Batch JKR4660 in 0.1 N HCl with 10% of alcohol	0	1	1	2	3	5	6	7
9 mg Batch JKR4660 in 0.1 N HCl with 20% of alcohol	3	6	9	12	16	19	22	25
9 mg Batch JKR4660 in 0.1 N HCl with 40% of alcohol	45	69	87	97	99	101	102	102

Table 11. Mean dissolution data of JKR4660 in Phosphate buffer pH 6.0 with alcohol

Batch Number/Time points (h)	0.25	0.5	0.75	1.25	1.5	1.75	2	3	4	6	8	10
9 mg Batch JKR4660 in Phosphate buffer pH 6.0 with 0% of alcohol	7	16	23	30	36	42	47	52	68	78	91	97

9 mg Batch JKR4660 in Phosphate buffer pH 6.0 with 5% of alcohol	10	26	39	50	59	67	74	79	92	98	100	101
9 mg Batch JKR4660 in Phosphate buffer pH 6.0 with 10% of alcohol	13	37	57	72	82	89	94	96	99	99	100	100
9 mg Batch JKR4660 in Phosphate buffer pH 6.0 with 20% of alcohol	14	37	60	78	89	96	99	100	102	102	102	102
9 mg Batch JKR4660 in Phosphate buffer pH 6.0 with 40% of alcohol	53	88	98	100	101	101	101	101	101	102	102	102

Table 12. Mean dissolution data of JKR4657 in 0.1 N HCl with alcohol

Batch Number/Time points (min)	15	30	45	60	75	90	105	120
6 mg Batch JKR4657 in 0.1 N HCl with 0% of alcohol	0	0	1	1	1	1	1	1
6 mg Batch JKR4657 in 0.1 N HCl with 5% of alcohol	1	1	1	1	1	1	1	2
6 mg Batch JKR4657 in 0.1 N HCl with 10% of alcohol	0	1	2	3	4	5	6	8
6 mg Batch JKR4657 in 0.1 N HCl with 20% of alcohol	2	5	8	11	14	17	20	22
6 mg Batch JKR4657 in 0.1 N HCl with 40% of alcohol	30	57	75	83	86	88	88	88

Table 13. Mean dissolution data of JKR4657 in Phosphate buffer pH 6.0 with alcohol

Batch Number/Time points (h)	0.25	0.5	0.75	1.25	1.5	1.75	2	3	4	6	8	10
6 mg Batch JKR4657 in Phosphate buffer pH 6.0 with 0% of alcohol	7	15	22	29	35	41	46	51	68	79	92	97
6 mg Batch JKR4657 in Phosphate buffer pH 6.0 with 5% of alcohol	12	28	40	50	59	66	72	77	91	95	98	98
6 mg Batch JKR4657 in Phosphate buffer pH 6.0 with 10% of alcohol	13	39	59	74	84	90	94	97	99	100	100	101
6 mg Batch JKR4657 in Phosphate buffer pH 6.0 with 20% of alcohol	17	46	71	87	95	99	100	100	101	101	102	95
6 mg Batch JKR4657 in Phosphate buffer pH 6.0 with 40% of alcohol	63	92	99	101	101	101	101	101	102	102	103	103

Figure 8. Comparative Dissolution Profiles of JKR4660 in 0.1 N HCl Containing 0%, 5%, 10%, 20%, and 40% alcohol

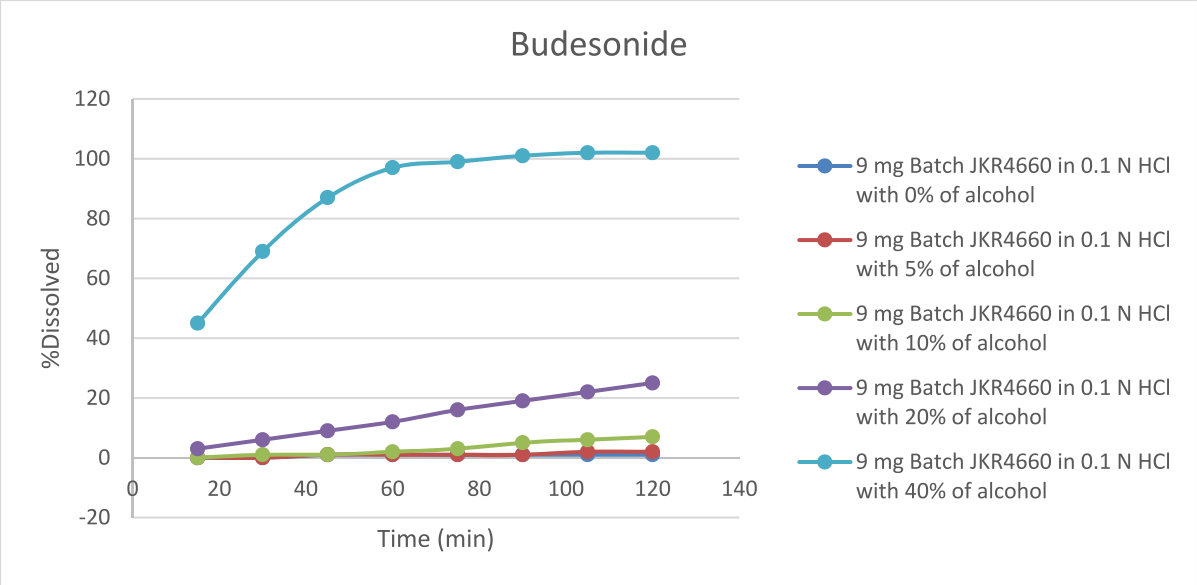


Figure 9. Comparative Dissolution Profiles of JKR4660 in Phosphate buffer pH 6.0 Containing 0%, 5%, 10%, 20%, and 40% alcohol

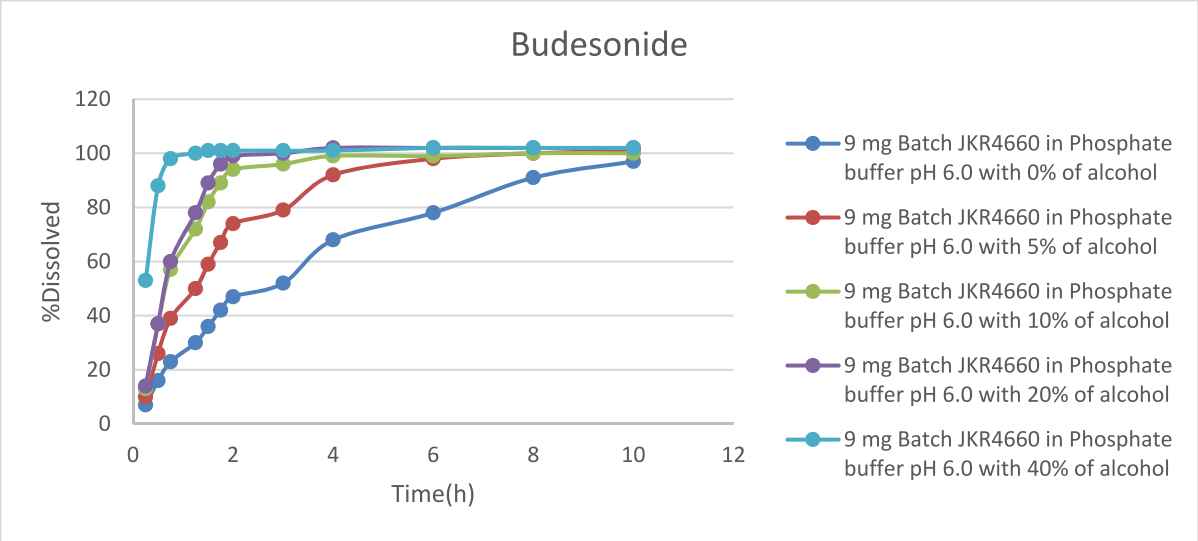


Figure 10. Comparative Dissolution Profiles of JKR4657 in 0.1 N HCl Containing 0%, 5%, 10%, 20%, and 40% alcohol

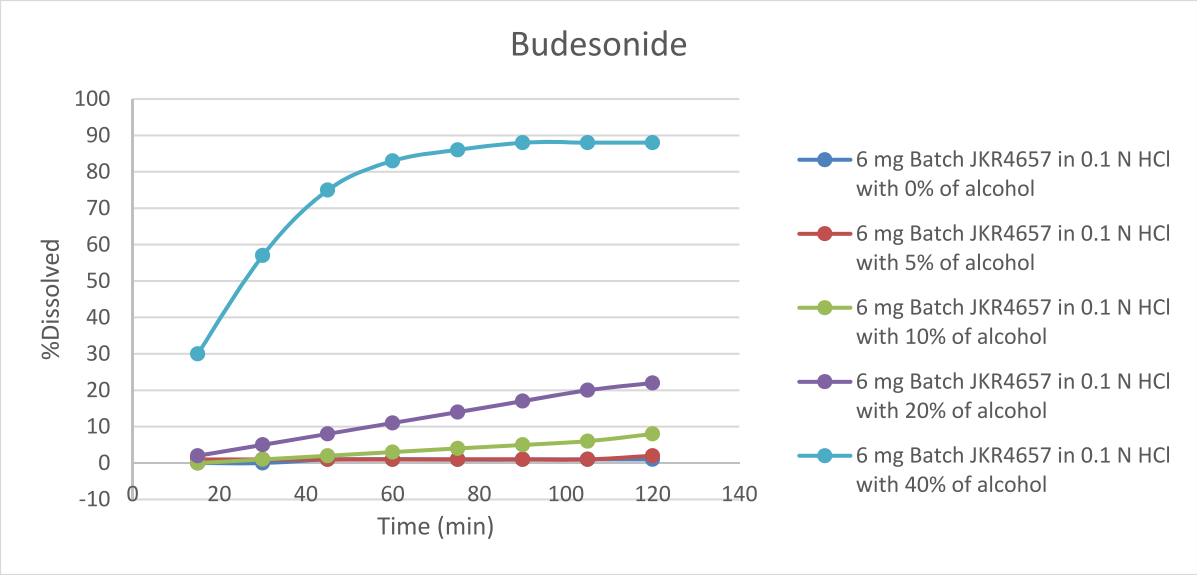
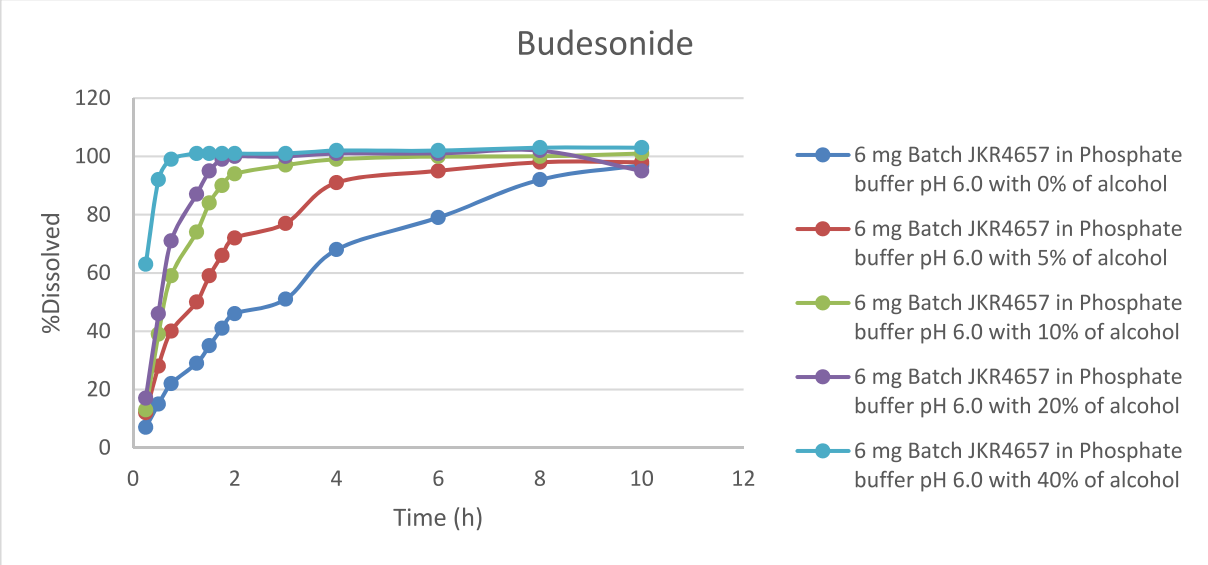


Figure 11. Comparative Dissolution Profiles of JKR4657 in Phosphate buffer pH 6.0 Containing 0%, 5%, 10%, 20%, and 40% alcohol



Reviewer's comment

The data in Tables 10-13 and Figures 7-10 show that both 40% and 20% alcohol cause faster release of Budesonide Capsules, 6 mg and 9 mg in 0.1 N HCl. Any amount of alcohol can cause faster release of *Budesonide Capsules, 6 mg and 9 mg in Phosphate buffer pH 6.0 based on the calculated similarity factors (f2 <50). In summary, alcohol can induce dose dumping of the proposed drug products.*

The above findings were conveyed to the clinical Pharmacology team.

Bridging of Formulations

Reviewer's Assessment: ***{Adequate}***

The commercial formulation is the same as the ones used in pivotal BE study.

Biowaiver Request

Reviewer's Assessment: ***{Adequate}***

The proposed products have two strengths: 9 mg and 6 mg. The Applicant conducted a bioequivalence study (under fasting conditions) to compare the higher strength of test product 9 mg (Batch JKR4660) with the Listed Drug- Entocort® EC (3×3 mg capsules, Batch FT0045), which is pending on Clinpharm Review conclusion (for additional details, please refer to clinical pharmacology review). The Applicant requested the biowaiver for the lower strength 6 mg.

A. BE study between the Listed Drug (3 mg x 3) and Test Product 9 mg

Study title: An open-label, single-dose, randomized, two-treatment, four-period, two-sequence, replicate crossover study in 48 healthy adult male (N=25) and female (N=23) subjects comparing the bioavailability of SPG's test formulation of Budesonide Capsules, 9 mg relative to that of an equal dose of Entocort® EC (3×3-mg capsules) under fasted conditions

The study results are listed in Table 14, which are pending on Clinical Pharm Review conclusion.

Table 14. Bioequivalence Analysis of Budesonide Capsules, 9 mg (Test) vs Entocort® EC Capsules, 3 × 3 mg (Reference) under Fasting Conditions (Study 11742615; N=48)

Parameter	Ratio of Least-Square Means for Test vs Reference (%)[a]	90% CI[b]
C_{max}	103.87	96.68-111.58
AUC_{0-t}	108.38	102.70-114.38
$AUC_{0-\infty}$	105.93	100.84-111.27

B. Formulation of the test products

Table 15. Qualitative and Quantitative Composition of the Drug Products

Components	Function	Compendial Reference	% w/w	mg/capsule 9 mg	mg/capsule 6 mg
(b) (4)					
Budesonide (Micronized)	Active	USP	(b) (4)	9.000	6.000
Ethyl cellulose Aqueous Dispersion (b) (4)					
Sucrose					
Acetyl tributyl citrate Polysorbate 80 (b) (4)					
Talc (b) (4)					
Methacrylic acid copolymer dispersion (b) (4)					
Triethyl Citrate					
Polysorbate 80 (b) (4)					
Simethicone Emulsion (b) (4)					
Talc (b) (4)					
(b) (4)					
Talc					
Encapsulation					
EHG Capsule, Size '1', Pink/Pink, Imprinted with '062'on Cap and Body in bk.	Hard Gelatin Capsule	--	--	(b) (4)	
EHG Capsule, Size '2', Light Grey/Pink, Imprinted with '061'on Cap and Body in bk.	Hard Gelatin Capsule	--	--		
		Total weight of Capsule	--	**448.360**	**311.240**

Table 15 shows that 9 mg strength and 6 mg strength are composition proportional.

C. Comparative dissolution assessment in multimedia at different rotation speeds

The Applicant conducted dissolution profile comparison between Biobatch JKR4660 and lower strength 6 mg Batch JKR4657 in multiple media: 0.1N HCl followed by pH 4.5 Acetate Buffer, pH 6.0 Phosphate Buffer, pH 6.8 Phosphate Buffer, and pH 7.5 Phosphate Buffer at different rotation speeds.

Table 16. Mean dissolution data between the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 75 rpm

Batch Number/Time points (h)	2	2.25	2.33	2.5	2.75	3	4	6	8	10
9 mg Batch JKR4660 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	0	1	1	2	3	4
6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	0	1	1	2	3	4
9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	11	14	20	28	36	57	79	89	92
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	10	13	20	28	35	55	76	85	91
9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	15	18	24	31	38	58	78	87	91
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	25	28	34	41	47	66	84	90	93
(b) (4)										
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5	1	22	25	31	38	45	64	83	92	96

Table 17. Mean dissolution data between the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 50 rpm

Batch Number/Time points (h)	2	2.25	2.33	2.5	2.75	3	4	6	8	10
9 mg Batch JKR4660 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	1	1	1	2	3	4
6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	0	0	1	2	3	4
9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	8	10	14	19	23	37	54	64	70
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	6	8	11	16	20	34	54	66	74
9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	9	10	14	18	22	34	51	63	70
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	15	17	20	24	28	41	57	67	72
(b) (4)										
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5	1	9	11	14	18	22	36	57	69	77

Table 18. Mean dissolution data between the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 100 rpm

Batch Number/Time points (h)	2	2.25	2.33	2.5	2.75	3	4	6	8	10
9 mg Batch JKR4660 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	1	1	1	2	3	4
6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5	1	0	0	0	1	1	1	2	3	4

9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	17	21	28	36	43	63	82	90	94
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0	1	10	14	22	31	39	63	85	93	96
9 mg Batch JKR4660 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	18	22	29	37	44	64	82	90	93
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8	1	25	28	35	43	51	73	92	95	94
										(b) (4)
6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5	1	18	22	29	38	47	66	85	92	94

Table 19. Dissolution Similarity Factors f2 between the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at different rotation speeds

Comparison	F2
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5 at 75 rpm	100
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0 at 75 rpm	83.54
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8 at 75 rpm	53.32
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5 at 75 rpm	57.79
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5 at 50 rpm	98.02
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0 at 50 rpm	78.27
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8 at 50 rpm	62.79
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5 at 50 rpm	68.92
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Acetate Buffer pH 4.5 at 100 rpm	100
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.0 at 100 rpm	67.10
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 6.8 at 100 rpm	59.34
9 mg Batch JKR4660 vs. 6 mg Batch JKR4657 in 0.1 N HCL followed by Phosphate buffer pH 7.5 at 100 rpm	93.03

Figure 12. Mean Comparative Dissolution Profiles of the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 75 rpm

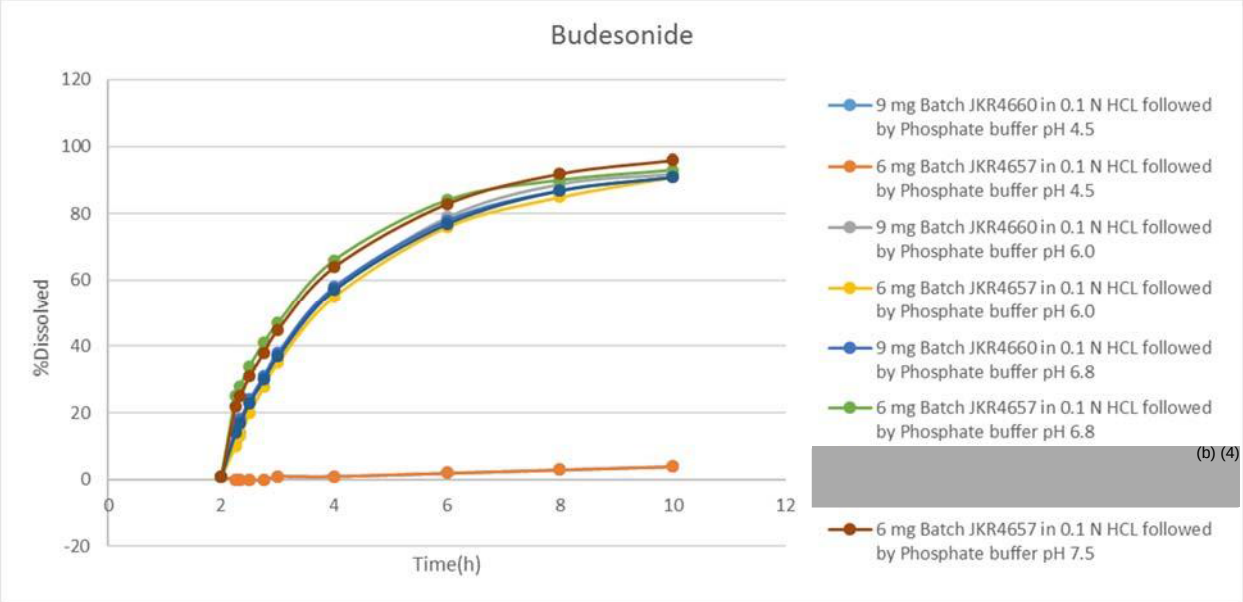


Figure 13. Mean Comparative Dissolution Profiles of the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 50 rpm

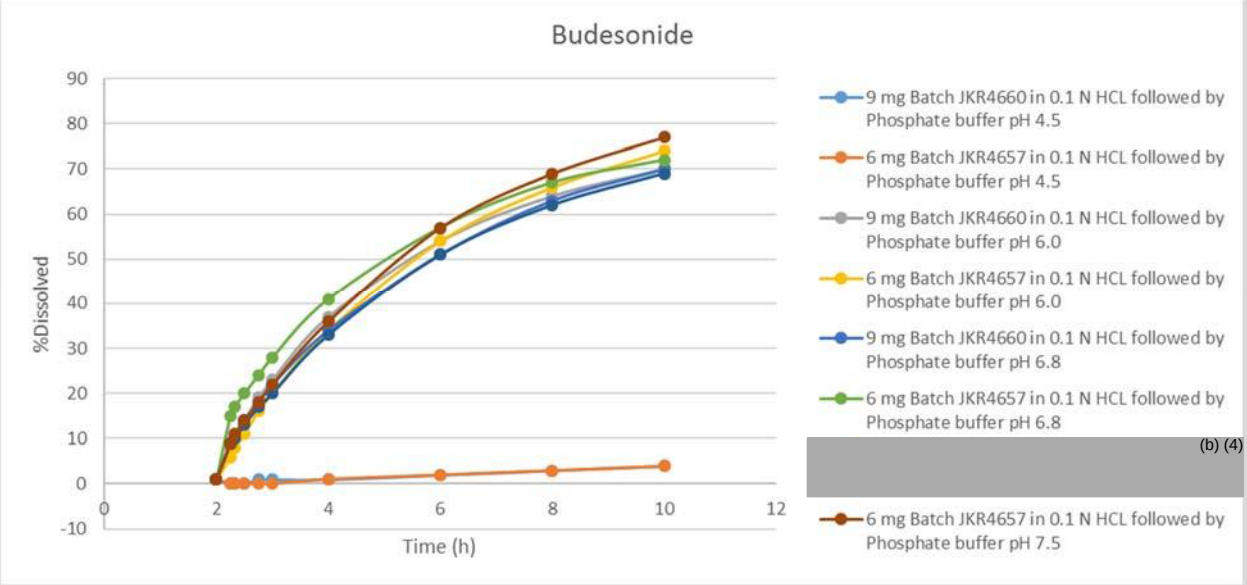
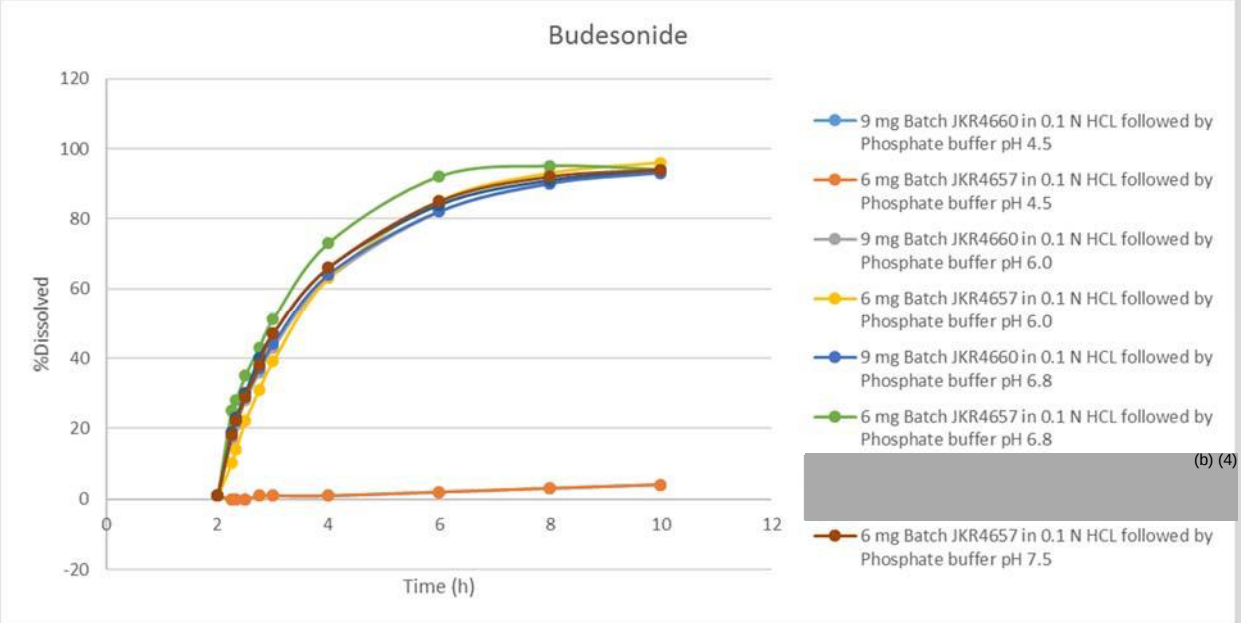


Figure 14. Mean Comparative Dissolution Profiles of the higher strength (JKR4660) and lower strength (JKR4657) in multimedia at 100 rpm



The calculated similarity factors shown in Table 17 indicate that the higher strength (JKR4660) and lower strength (JKR4657) are similar on dissolution profiles in multimedia at different rotation speeds.

C. Biowaiver

Provided bioequivalence is demonstrated between the 9 mg strength test product and the Listed Drug-Entocort® EC (3×3 mg capsules), the biowaiver is granted for the lower strength 6 mg due to the following reasons:

1) The lower strength product is in the same dosage form, but in different strength.

2) The lower strength (6 mg) and the higher strength (9 mg) are proportionally similar in its active and inactive ingredients.

3) The lower strength (6 mg) and the higher strength (9 mg) are similar on dissolution profiles in multimedia at different rotation speeds.

R Regional Information

Comparability Protocols

Reviewer's Assessment:

N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment:

N/A

Lifecycle Management Considerations

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, PharmD, Ph.D., 11/8/2018

Biopharmaceutics reviewer

OPQ/ONDP/DB

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Tien-Mien Chen, Ph.D. I concur. 11/14/18
Acting Biopharm Lead.
DB/ONDP/OPQ

LABEL FOR NDA 211929

I. PI

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) **safely and effectively. See full prescribing information for** (b) (4)

BUDESONIDE (b) (4) **for oral use**
Initial U.S. Approval: 1997

---------- INDICATIONS AND USAGE ----------

(b) (4) is a corticosteroid indicated for:

- Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older. (1.1)
- Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Administration Instructions (2.1):

- Take once daily in the morning.
- Swallow whole. Do not chew or crush.
- Avoid consumption of grapefruit juice for the duration of therapy.

Recommended Dosage:

Mild to moderate active Crohn's disease (2.2):

- Adults: 9 mg once daily for up to 8 weeks; repeat 8 week treatment courses recurring episodes of active disease.
- Pediatrics 8 to 17 years who weigh more than 25 kg: 9 mg once daily for up to 8 weeks, followed by 6 mg once daily in the morning for 2 weeks.

Maintenance of clinical remission of mild to moderate Crohn's disease (2.3):

- Adults: 6 mg once daily for up to 3 months; taper to complete cessation after 3 months. Continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.
- When switching from oral prednisolone, begin tapering prednisolone concomitantly with initiating (b) (4)

----------DOSAGE FORMS AND STRENGTHS----------

(b) (4) 6 mg and 9 mg (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to budesonide or any of the ingredients in (b) (4) (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypercorticism and Adrenal Axis Suppression: Follow general warnings concerning corticosteroids and paediatrics and patients with hepatic impairment may be at increased risk. (5.1, 8.4)
- Symptoms of Steroid Withdrawal in Patients Transferred from Other Systemic Corticosteroids: Taper slowly from corticosteroids with high systemic effects; monitor for withdrawal symptoms and unmasking of allergies (rhinitis, eczema). (5.2)
- Increased Risk of Infection, including Serious and Fatal Chicken Pox and Measles: Monitor patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. (5.3)
- Other Corticosteroid Effects: Monitor patients with concomitant conditions where corticosteroids may have unwanted effects (e.g., hypertension, diabetes mellitus). (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥ 5%) in adults are: headache, respiratory infection, nausea, back pain, dyspepsia, dizziness, abdominal pain, flatulence, vomiting, fatigue, and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sun Pharmaceutical Industries, Inc. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

CYP3A4 Inhibitors (e.g., ketoconazole, grapefruit juice): Can increase systemic budesonide concentrations: avoid use. (2.1, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	**Budesonide** (b) (4)	**Adequate** **No tradename is proposed**
Dosage form, route of administration	(b) (4) **for oral use**	**Not Adequate** The proposed drug product formulation contains both delayed-release and extended-release. It is a 505b(2) with RLD of Entocort EC (NDA 21324). The Agency has decided that Entocort EC should revise the dosage form from (b) (4) to "extended-release capsules". Therefore, this new dosage terminology for the current proposed drug product should be the same as Entocort EC capsules using "extended-release capsuels"
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	(b) (4) 6 mg and 9 mg	**Not Adequate** **The dosage form should be revised to extended-release capsules**

This section is not adequate.

- **Budesonide** (b) (4) should be revised to:

  Budesonide Extended-Release capsules

2. ***Section 2 Dosage and Administration***

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

- Take [redacted] (b) (4) once daily in the morning.
- Swallow [redacted] (b) (4) whole. Do not chew or crush.
- Avoid consumption of grapefruit juice for the duration of [redacted] (b) (4) therapy *[see Drug Interactions (7.1)]*.

2.2 Treatment of Mild to Moderate Active Crohn's Disease

The recommended dosage of [redacted] (b) (4) is:

Adults: 9 mg orally once daily for up to 8 weeks. Repeated 8 week courses of [redacted] (b) (4) can be given for recurring episodes of active disease.

Pediatric patients 8 to 17 years who weigh more than 25 kg: 9 mg orally once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks.

2.3 Maintenance of Clinical Remission of Mild to Moderate Crohn's Disease

The recommended dosage in adults, following an 8 week course(s) of treatment for active disease and once the patient's symptoms are controlled (CDAI less than 150), is [redacted] (b) (4) 6 mg orally once daily for maintenance of clinical remission up to 3 months. If symptom control is still maintained at 3 months an attempt to taper to complete cessation is recommended. Continued treatment with [redacted] (b) (4) 6 mg for more than 3 months has not been shown to provide substantial clinical benefit.

Patients with mild to moderate active Crohn's disease involving the ileum and/or ascending colon have been switched from oral prednisolone to [redacted] (b) (4) with no reported episodes of adrenal insufficiency. Since prednisolone should not be stopped abruptly, tapering should begin concomitantly with initiating [redacted] (b) (4) treatment.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	• Take [redacted] (b) (4) once daily in the morning. • Swallow [redacted] (b) (4) whole. Do not chew or crush. • Avoid consumption of grapefruit juice for the duration of [redacted] (b) (4) therapy *[see Drug Interactions (7.1)]*.	**Not Adequate** **The dosage form should be revised to "extended-release capsules"**

This section is not adequate.

- [redacted] (b) (4) should be revised to:

(b) (4)

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

(b) (4).

- 6 mg: hard gelatin capsules with light grey colored cap and pink colored body imprinted with "061" on cap and body in black ink containing white to off-white pellets.
- 9 mg: hard gelatin capsules with pink colored cap and pink colored body imprinted with "062" on cap and body in black ink containing white to off-white pellets.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	(b) (4)	**Not Adequate should be revised to "extended-release capsules"**
Strengths: in metric system	6 mg, 9 mg	**Adequate**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	• 6 mg: hard gelatin capsules with light grey colored cap and pink colored body imprinted with "061" on cap and body in black ink containing white to off-white pellets. • 9 mg: hard gelatin capsules with pink colored cap and pink colored body imprinted with "062" on cap and body in black ink containing white to off-white pellets.	**Adequate**

This section is not adequate.

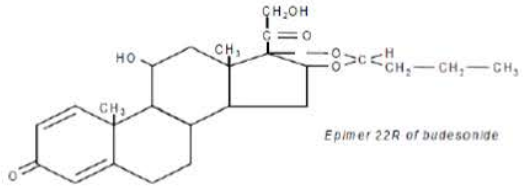
- The dosage form should be revised to:

"Extended-Release capsules"

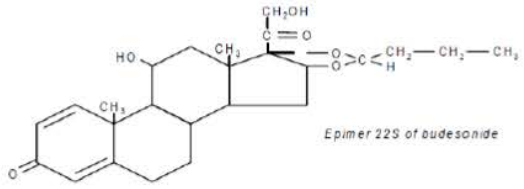
4. *Section 11 Description*

11 DESCRIPTION

Budesonide, the active ingredient in [redacted] (b) (4) is a synthetic corticosteroid. Budesonide is designated chemically as (RS)-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The molecular formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Epimer 22R of budesonide



Epimer 22S of budesonide

Budesonide is a white to off-white powder that is practically insoluble in water and heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 5 is 1.6 x 10^3 ionic strength 0.01.

Each [redacted] (b) (4) for oral administration contains 6 mg and 9 mg of budesonide, USP (micronized) with the following inactive ingredients: acetyl tributyl citrate, corn starch, ethylcellulose aqueous dispersion, methacrylic acid and ethyl acrylate copolymer dispersion, polysorbate 80, simethicone emulsion, sucrose, talc, and triethyl citrate.

Capsule shell contains gelatin, iron oxide black (for 6 mg), iron oxide red, iron oxide yellow, sodium lauryl sulphate and titanium dioxide.

The imprinting ink contains black iron oxide, potassium hydroxide and shellac.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4)	**Not Adequate** **Established name should be revised to "Budesonide Extended-Release Capsules"**
Dosage form and route of administration	Each (b) (4) for oral administration…	**Not Adequate** **The 2nd paragraph should start with each extended-release capsule…**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	…inactive ingredients: sucrose, corn starch, ethylcellulose aqueous dispersion, acetyl tributyl citrate, polysorbate 80, talc, methacrylic acid and ethyl acrylate copolymer dispersion, triethyl citrate and simethicone emulsion. Capsule shell contains gelatin, sodium lauryl sulfate, titanium dioxide, iron oxide red, iron oxide black (for 6 mg) and iron oxide yellow. The imprinting ink contains shellac, black iron oxide and potassium hydroxide.	**Adequate**
Statement of being sterile (if applicable)	N/A	**Adequate**
Pharmacological/ therapeutic class	…synthetic corticosteroid…	**Adequate**
Chemical name, structural formula, molecular weight	Provided	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Provided as described in the Entocort® EC	**Adequate**

This section is not adequate. The following revision should be made:

- The established name should be revised to:

  "Budesonide Extended-Release Capsules"
- Dose strength should be changed to read "each extended-release capsule …contains 6 mg or 9 mg…"

5. *Section 16 How Supplied/Storage and Handling*

16 HOW SUPPLIED/STORAGE AND HANDLING

- (b) (4) 6 mg are hard gelatin capsules with light grey colored cap and pink colored body imprinted with "061" on cap and body in black ink containing white to off-white pellets.

  Bottles of 30's with Child Resistant Cap.....NDC 47335-315-83
  Bottles of 100's with Child Resistant Cap.....NDC 47335-315-88
  Bottles of 500's with Non Child Resistant Cap.....NDC 47335-315-13

- (b) (4) 9 mg are hard gelatin capsules with pink colored cap and pink colored body imprinted with "062" on cap and body in black ink containing white to off-white pellets.

  Bottles of 30's with Child Resistant Cap.....NDC 47335-316-83
  Bottles of 100's with Child Resistant Cap.....NDC 47335-316-88
  Bottles of 500's with Non Child Resistant Cap.....NDC 47335-316-13

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep container tightly closed.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	(b) (4) 6 mg… 9 mg…	**Not Adequate** Dosage form should be changed to extended-release capsules
Available units (e.g., bottles of 100 tablets)	Bottles of 30's, 100' and 500's.	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4) 6 mg are hard gelatin capsules with light grey colored cap and pink colored body imprinted with "061" on cap and body in black ink containing white to off-white pellets. (b) (4) 9 mg are hard gelatin capsules with pink colored cap and pink colored body imprinted with "062" on cap and body in black ink containing white to off-white pellets.	**Adequate**
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Keep container tightly closed.	**Adequate**
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]	**Adequate**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not provided	**Not Adequate** **Add** Manufacturer/distributor name

This section is not adequate. The following revision should be made:

- Dosage form should be changed to extended-release capsules
- Add Manufacturer/distributor name

II. Labels:

1. Immediate Container Label


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	**Not Adequate** The established name should be revised to "Budesonide Extended-release Capsules"
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	6 mg or 9 mg	**Adequate**
Net contents	30, 100 or 500 capsules	**Adequate**
"Rx only" displayed prominently on the main panel	Provided	**Adequate**
NDC number (21 CFR 207.35(b)(3)(i))	Provided	**Adequate**
Lot number and expiration date (21 CFR 201.17)	Provided	**Adequate**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. (b) (4) Dispense in a tight, light-resistant, and child-resistant containers (USP)	**Adequate**
Bar code (21CFR 201.25)	Provided	**Adequate**
Name of manufacturer/distributor	Provided	**Adequate**
And others, if space is available	**KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN**	**Adequate**

This section is not adequate. The following revision should be made:

- The proprietary name (if proposed), established name should be revised with the new dosage form nomenclature as following:

Budesonide Extended-Release Capsules

2. **Carton Label**

Not proposed

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

- Budesonide (b) (4) should be revised to: Budesonide Extended-Release Capsules

II. Full Prescribing Information

For Section 2, "DOSAGE AND ADMINISTRATION"

- (b) (4)

For section 3, "DOSAGE FORM AND STRENGTH"

- The dosage form should be revised to: "Extended-Release Capsules"

For Section 11, "DESCRIPTION"

- The established name should be revised to: "Budesonide Extended-Release Capsules"
- Dose strength should be changed to read "each extended-release capsule …contains 6 mg or 9 mg…"

For Section 16, "HOW SUPPLIED/STORAGE AND HANDLING"

- Dosage form should be revised to (b) (4)
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:

Immediate Container label

- The proprietary name, established name, dosage form and strength should be revised as following:

  Budesonide Extended-Release Capsules

Overall Assessment and Recommendation:

The labeling and labels are **not** deemed ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the deficiencies are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.
Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Zhengfang Ge's assessment on the labels and labeling, and her recommendation that this application is not ready for approval in its present form until the delineated deficiencies are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.
Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 11/30/2018 12:27:00PM
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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
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Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 211929 Budesonide Extended Release Capsules, 6 mg and 9 mg

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking		Risk Evaluation	LifeCycle consideration/Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters	L		Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Low to None	None