CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213976Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	213976
Applicant Name	Takeda Pharmaceuticals U.S.A. Inc.
Drug Product Name	EOHILIA® (budesonide oral suspension)
Dosage Form	Oral Suspension
Proposed Strength(s)	2 mg/10 mL
NDA Classification	Type 3 - New Dosage Form
Route of Administration	Oral
Maximum Daily Dose	4 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of Eosinophilic Esophagitis (EoE) (b) (4) (b) (4) in patients 11 years and older.
Drug Product Description	The applicant, Takeda Pharmaceuticals U.S.A., submitted this 505(b)(2) application for Eohilia® (budesonide oral suspension), 2 mg/10mL (0.2 mg/mL) indicated for the treatment of eosinophilic esophagitis (EoE), (b) (4) (b) (4) in adult and adolescent patients 11 years and older. Eohilia is provided as 2 mg in 10-mL unit-dose child-resistant packets. The patients are to take the unit-dose containing 2 mg of budesonide twice daily. The active ingredient, budesonide, is a corticosteroid with anti-inflammatory effects with high affinity to glucocorticoid receptors is a white or almost-white, crystalline powder that is freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in water and heptane. Budesonide was first approved in1994 as the active ingredient of brand name drug

	product RHINOCORT® under NDA 020233. Since the original approval, multiple brand name and generic drug products containing this active ingredient have been approved for marketing in the United States. Entocort EC (budesonide) delayed-release capsules (NDA 021324) has been proposed as the listed drug (LD) for this application. Eohilia (budesonide oral suspension) is a white to yellow viscous suspension that contains 2 mg of budesonide in 10-mL unit-dose as the active ingredient and acesulfame potassium, ascorbic acid, Avicel® RC 591, cherry flavor, citric acid, dextrose, disodium EDTA, glycerin, Magnasweet® 110, maltodextrin, polysorbate 80, potassium sorbate, sodium ascorbate, sodium benzoate, sodium citrate, and purified water as inactive ingredients. Eohilia will be marketed in cartons containing 60-count 2 mg/10 mL unit-does packets providing 30-day supply for twice daily oral administration. This drug product should be stored at 2ºC to 25ºC (36°F to 77°F) with excursions permitted up to 30°C (86°F) (b) (4) Do not Freeze this product. Based on the additional stability data provided in this resubmission, an expiration dating period of 36 months is granted for this drug product. This application was submitted as a rolling review on October 15, 2020, as a breakthrough therapy application with the priority review. However, this application received a completed response on December 17, 2021. This application was resubmitted as a class 2 resubmission on August 22, 2023.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	2°C to 25°C (36°F to 77°F).		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
	Drug Product/ Labeling	Hamid Shafiei, Ph.D.	Nina Ni, Ph.D. Julia Pinto, Ph.D.
	Manufacturing	Khalid Khan, Ph.D.	Cassandra Abellard, Ph.D.
	Biopharmaceutics	Kaushalkumar Dave, Ph.D.	Tapash Ghosh, Ph.D.
	Microbiology	Yan Zheng, Ph.D.	Jesse Wells, Ph.D.
	Other: Environmental Assessment	Venkateswara Pavuluri, Ph.D.	Wendy Wilson-Lee, Ph.D.
	RBPM	Megan Nguyen	
	ATL	Hamid Shafiei, Ph.D.	
Consults	N/A		

2. Final Overall Recommendation - ***Approval*** *pending submission of the final PI labeling and container and carton labels to the application (all CMC recommended changes have been accepted by the applicant).*

4. Basis for Recommendation:

This application was originally submitted as a rolling review submission which was completed on October 15, 2020. This application received a complete response from clinical perspective. To responds to the complete response and resubmit this application, the applicant requested an extend to December 17, 2023. This application was resubmitted on August 22, 2023, as a class II resubmission. Due to the complete response the labeling negotiations were not pursed during the first review cycle and therefore, this application was not recommended for approval from the OPQ perspective due CMC labeling/labels deficiencies.

This resubmission included minor updates to drug substance, drug product, and manufacturing that have been review and found adequate. No updates to the pharmaceutics and microbiology section of this NDA was submitted in this resubmission, and the IQA for this submission will not include biopharmaceutics and microbiology review chapters.

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, budesonide, and drug product, Eohilia® (budesonide oral suspension), 2 mg/10mL (0.2 mg/mL).

- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.

- The CMC revisions on labels/labeling have been communicated to the applicant and the recommended CMC revisions have been accepted by the applicant.

- The applicant's request for categorical exclusion from preparation of environmental assessment has been found adequate and is granted.

Therefore, from the OPQ perspective this application is recommended for approval with an expiration dating period of 36 months pending the submission of the final PI labeling and container and carton labels to the application.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Choose an item.

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
Branch IV/DNDP II/ONDP/OPQ

Memorandum

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

Date: **February 2, 2024**

From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products II
Office of New Drug Products

To: **To Labeling Review Chapter (dated 12/14/2023) for NDA 213976**

Subject: **Recommendation – Labeling Chapter for NDA 213976 - Adequate**

At the conclusion of the firs review cycle this application received a complete response on December 17, 2021 from the clinical perspective. Therefore, the labeling negotiations were not pursued during the first review cycle. This application was resubmitted on August 22, 2023 as a Class II resubmission.

Although the resubmission was intended to provide the requested clinical information to appropriately respond to the complete response letter, it also included updates to the CMC sections of the application. This resubmission included minor updates to drug substance, drug product, and manufacturing process. The CMC updates were reviewed and found adequate. During this review cycle the labeling negotiations were pursued and the CMC-recommended revisions to the PI labeling as well as container closure and carton labels were communicated to the applicant. The applicant accepted CMC-recommended revisions. However, to ensure this drug will be available to the patients with no further delays, some of the editorial changes have been deferred to the post-approval. For example, the Agency recommended revision of the dosage and packaging description from “single-does stick pack” to “unit-dose packets” is one of the revisions that will be adopted post-approval. The applicant intends to submit a prior approval supplement post-approval to adopt all remaining revisions recommended by the Agency. This will allow the patients to receive the drug while the changes to labeling are made.

Therefore, based on the applicant’s commitment to adopt the Agency recommended revisions post-approval, the current PI labeling as well as container closure and carton labels are considered adequate to support the approval of this application from the labeling perspective.

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	213976
Assessment Cycle Number	2
Drug Product Name	EOHILIA™ (budesonide oral suspension)

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	Inadequate	
Instruction for Use (IFU)	Inadequate	
Container Labels	Inadequate	
Carton Labeling	Inadequate	

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SDN 64	08/22/2023	Resubmission with latest proposed labeling

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	budesonide oral suspension
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	Oral
Initial U.S. Approval [§201.57(a)(3)]	Adequate	1997
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Oral suspension: 2mg/10mL
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	N/A
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	N/A

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	Inadequate	single-dose stick packs should be change to unit-dose packets

Assessment: *Inadequate*

Single-dose stick packs should be revised to unit-dose packets.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Inadequate	(b) (4)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	N/A
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare	N/A	N/A

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

Assessment: *Inadequate*

(b) (4)

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Oral suspension
Strength(s) in metric system	Adequate	2 mg/10 mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and	Inadequate	White to yellow, cherry flavored, (b) (4) viscous suspension (b) (4) 10 mL single-dose stick packs. However, single-dose stick

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
color and clarity of the solution, when applicable.		packs should be change to unit-dose packets.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Inadequate*

Single-dose stick packs should be revised to unit-dose packets.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Inadequate	Needs to be revised to: EOHILIA (budesonide oral suspension) contains budesonide, a synthetic (b) (4) corticosteroid.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid	Inadequate	The placement of Avicel® RC 591, ascorbic acid in the list of inactive ingredients should be switched to correctly maintain alphabetical order.

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients,

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
brand names. [§ 201.57(c)(12)(i)(C)].		
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (if applicable).	Adequate	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by	N/A	

recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Drug Company X," "structurally unique molecular entity").		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Inadequate*

In the description the Trade Name and established name presentation should be revised to :

EOHILIA (budesonide oral suspension) contains budesonide, a synthetic (b) (4) corticosteroid.

The list of inactive ingredients should be revised to switch the placement of Avicel® RC 591 and ascorbic acid to maintain alphabetical order.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Should be revised to unit-dose packets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x	Adequate	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Need to add excursion permitted (b) (4) to 30°C
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	

Assessment: *Inadequate*

The available units should be revised to unit-dose packets.

The storage condition should be revised to include "excursion permitted (b) (4) to 30°C".

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Distributed by:

Takeda Pharmaceuticals America, Inc.

Lexington, MA 02421

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

This section of the labeling is adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Inadequate	Need to add excursion permitted (b) (4) to 30°C
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	The placement of Avicel® RC 591, ascorbic acid in the list of inactive ingredients should be switched to correctly maintain alphabetical order.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Inadequate*

The placement of Avicel® RC 591 and ascorbic acid in the list of inactive ingredients should be switched to correctly maintain alphabetical order.

The storage condition should be revised to include "excursion permitted (b) (4) to 30°C".

3.0 CONTAINER AND CARTON LABELING[25]

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources

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

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Inadequate	Yes	The single-dose stick packs should be revised to unit-dose packets
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	Yes	Need to add excursion permitted (b) (4) 30°C

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Inadequate	No	Inactive ingredient is not provided on the packet labels due to the limited space and it is not required. However, on the carton labels the placement of Avicel® RC 591, ascorbic acid in the list of inactive ingredients should be switched to correctly maintain alphabetical order
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance	N/A	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]			
And others if space is available.	Adequate	Yes	

Assessment of Carton Labels and Container Labeling: *Inadequate*

- Single-does stick packs should be revised to unit-dose packets
- The placement of Avicel® RC 591 and ascorbic acid in the list of inactive ingredients should be switched to correctly maintain alphabetical order.
- Storage condition should be revised to include "excursion permitted (b) (4) to 30°C".

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

- Single-use stick packs should be replace with unit-dose packets throughout the Prescribing Information, Patient Information, IFU, as well as container and carton labels.
- In Section 11 of the Prescribing Information, Patient Information, IFU, carton label and/or wherever the inactive ingredients are listed, the placement of Avicel® RC 591 and ascorbic acid should be switched to accurately maintain the alphabetical order.
- In section 11 of the Prescribing Information the following change to the description is recommended:

  EOHILIA (budesonide oral suspension) contains budesonide, a synthetic corticosteroid.
- In section 16 of the PI, Patient Information, on container and carton labels, and wherever applicable, the storage condition should be revised to include excursion permitted (b) (4) to 30°C.

[31] USP General Notices 3.20 Indicating Conformance

Therefore, this application is not recommended for approval in its current form until the CMC delineated changes to labeling/labels are appropriately addressed 21 CFR 314.125(b)(6).

Primary Labeling Assessor Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
Branch 4/DNDP 2/OPQ

Secondary Assessor Name and Date:

Julia Pinto, Ph.D.
Branch Chief
Branch 3/DNDP 2/OPQ

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 12/14/2023 11:10:25AM
GUID: 507d824300005f344cf8b5e5989f0057

Julia Pinto

Digitally signed by Julia Pinto
Date: 12/14/2023 11:11:19AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
02/02/2024 11:13:40 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213976
EOHILIA (budesonide oral suspension)
Assessment #1

Drug Product Name	EOHILIA (budesonide oral suspension)
Dosage Form	oral suspension
Strength	2 mg / 10 mL (0.2 mg/mL) single-dose stick pack
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Takeda Pharmaceuticals U.S.A. Inc.
US agent, if applicable	Not Applicable

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001(Starting of the Rolling Submission)	08/31/2020	Biopharmaceutics
Original Submission (0004)	10/15/2020	Drug Substance, Drug Product, OPMA, Biopharmaceutics, Micro, Labeling, EA Team
Amendment (0006)	11/12/2020	Micro
Amendment (0009)	11/30/2020	Drug Product, OPMA
Amendment (0012)	12/16/2020	Drug Product, Micro, OPMA
Amendment (0014)	12/21/2020	Drug Product, Micro, OPMA
Amendment (0016)	12/23/2020	Biopharmaceutics, OPMA
Amendment (0024)	02/02/2021	OPMA
Amendment (0025)	02/05/2021	Biopharmaceutics
Amendment (0029)	02/19/2021	OPMA
Amendment (0031)	02/24/2021	Drug Product, OPMA
Amendment (0033)	03/03/2021	Biopharmaceutics, OPMA
Amendment (0034)	03/05/2021	OPMA
Amendment (0035)	03/10/2021	OPMA
Amendment (0037)	03/24/2021	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Gaetan Ladouceur	Donna Christner
Drug Product	Venkateswara Pavuluri	Wendy Wilson-Lee
Manufacturing	Khalid Khan	Frank Wackes
Microbiology	Yan Zheng	Jesse Wells
Biopharmaceutics	Kaushalkumar Dave	Tapash Ghosh
Regulatory Business Process Manager	Marquita Burnett	
Application Technical Lead	Hong Cai, Ph.D.	
Laboratory (OTR)	-	-
Environmental	Venkateswara Pavuluri	Wendy Wilson-Lee
Labeling	Venkateswara Pavuluri	Wendy Wilson-Lee

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

As of this review, Takeda Pharmaceuticals U.S.A. Inc. 505(b)(2) New Drug Application #213976, for EOHILIA (budesonide oral suspension), 2 mg/10 mL (0.2 mg/mL) single-dose pack, is not ready for approval in its present form per 21 CFR 314.125(b)(8).

Because a clinical "Discipline Review Letter" issued on 03/19/2021 in which the deficiencies related to the product efficacy had been identified, the negotiation of the labeling (the Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU) and Container/Carton Labels documents) has not been completed and the labeling related issues have not been resolved. In its present form, the labeling does not comply with 21 CFR 201.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, and purity of the drug product. Adequate drug substance, drug product, manufacturing process and facilities, and the product quality microbiology information has been provided. From the biopharmaceutics perspective, suitable controls for in vitro dissolution have been established.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 29, 2021. The recommendation remains current as of this review.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Takeda Pharmaceuticals U.S.A. (Takeda or formerly Shire) submitted a 505(b)(2) NDA 213976. The proposed drug product is budesonide oral suspension (BOS) with the proposed proprietary name as Eohilia.The active ingredient is budesonide which is an anti-inflammatory corticosteroid with high affinity to glucocorticoid receptors. The proposed indication is for the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older. The listed drug for NDA 213976 is Entocort EC (budesonide) delayed-release capsules (NDA 021324).

On May 31, 2016, Eohilia was granted a Breakthrough Therapy Designation (BTD) for the treatment of patients with eosinophilic esophagitis under IND 103173. The Applicant completed the rolling submission of NDA 213976 on October 15, 2020. This NDA is a priority review.

Eohilia (budesonide oral suspension) is a white to yellow, cherry flavored, thixotropic, viscous suspension with 0.2 mg/mL of (b) (4) budesonide. Eohilia is an immediate release dosage form. Eohilia is available as a 10 mL unit dose stick pack (2 mg/unit) and packaged as 60 units in a (b) (4) carton. The proposed dose of Eohilia is 2 mg orally twice daily (morning and evening). Therefore, each carton contains a 30-day supply.

The to-be marketed formulation is SB-10. The formulation for the phase 3 clinical study is MB-9. The only difference is the addition of (b) (4) (b) (4) (sodium ascorbate and ascorbic acid) to SB-10 with the total amount of (b) (4) %w/w. (b) (4) (b) (4) There is no concern from quality perspective with the above formulation change. Note that the Applicant performed a comparative bioavailability study (SHP621-101) to generate PK bridging data between the two formulations (MB-9 and SB-10). It appears that the in vivo bioequivalent is demonstrated. Details refer to the ClinPharm assessment.

The drug substance budesonide manufacturer for the commercial production is (b) (4) The drug product Eohilia is manufactured at (b) (4) (b) (4)

The expiration dating period is 24 months when Eohilia is stored at (b) (4) ºC to 25ºC (b) (4) °F to 77°F) with excursions permitted from (b) (4) °C to 30°C (b) (4) °F to 86°F) (b) (4) Do not Freeze.

Proposed Indication(s) including Intended Patient Population	For the treatment of eosinophilic esophagitis (EoE), (b) (4) in adult and adolescent patients 11 years and older
Duration of Treatment	As needed
Maximum Daily Dose	2 mg twice daily for oral administration
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance budesonide is a white or almost white, odorless, crystalline powder, practically insoluble in water, freely soluble in chloroform. Note that no polymorphic forms have ever been observed and the drug substance is a mixture of the C-22S (epimer A) and the C-22R (epimer B).

The applicant has cross-referenced to Type II DMF (b) (4) (the holder is (b) (4) and DMF (b) (4) (the holder is (b) (4) (b) (4) for budesonide drug substance CMC information. DMF (b) (4) and DMF (b) (4) were last reviewed by the Agency on 01/25/2021 and on 07/29/2020 respectively and both have been found adequate. The retest period is (b) (4) months for the drug substance when stored at (b) (4) (b) (4)

The drug substance reviewer Dr. Gaetan Ladouceur finds the information on the drug substance budesonide is adequate to support the approval of the NDA. See IQA Chapter I Drug Substance for details.

Drug Product: Adequate

Eohilia oral suspension (SB-10) is supplied as unit-dose stick packs to hold a nominal volume of 10 mL with 60 packs per carton. Eohilia also contains the following excipients: (b) (4) (Avicel RC-591) and maltodextrin (b) (4) dextrose (b) (4) disodium EDTA (b) (4) citric acid and sodium citrate (b) (4) (b) (4), polysorbate 80 (b) (4) glycerin (b) (4) (b) (4), sodium ascorbate and ascorbic acid ((b) (4) sodium benzoate and potassium sorbate ((b) (4) acesulfame potassium and magnasweet 110 (b) (4) cherry flavor and purified water. Except the cherry flavor and Magnasweet® 110 ((b) (4) (b) (4), all excipients present in the formulation are of compendial grade (USP/NF) and acceptable. The in-house specifications and test methods for the two non-compendial excipients are established and also acceptable.

The proposed specification for the drug product includes tests for appearance, identification (UV and HPLC retention times), assay and uniformity of dosage units, the related substances, dissolution, pH, assay of the (b) (4) and the (b) (4) viscosity and the microbiological examinations (TAMC, TYMC and BCC). The proposed acceptance criteria for all the attributes are acceptable from the quality perspective. Note that the known related substance (b) (4) a potential genotoxic impurity formed via (b) (4), is

controlled at NMT (b) (4) %LC which equates to a daily intake of (b) (4) µg/day. and this is acceptable. This is based on the qualification study and the agreement between the Applicant and the Agency (Refer to Pre-NDA Type B CMC meeting minutes of IND 103173 dated May 21, 2020 and Non-Clinical review by Dr. Yolanda Branch dated March 18, 2021). The applicant's proposal of not including the tests for elemental impurities and the (b) (4) in drug product release specification are acceptable based on the manufacturing procedures and the risk assessments per ICH guidelines. The results of the leachables test of the proposed packaging system in three primary registration batches are below the calculated AET levels both at release and during stability testing. Therefore, omitting routine leachables testing at batch release and in future stability testing is acceptable from quality (CMC) perspective.

The batch data for the registration batches as well as supportive clinical batches all conform to the specifications. The analytical methods used in analysis of the drug product batches, at release and in stability studies, were suitably validated and deemed adequate for the intended purpose.

Stability data provided to date support a 24-month shelf-life when the drug product is packed in the proposed container and closure systems and stored at (b) (4) to 25°C (b) (4) to 77°F) with excursions permitted from (b) (4) to 30°C (b) (4) °F to 86°F). Do not freeze.

The applicant has requested a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b). While approval of this NDA for EoE indication will increase use, the expected introduction concentration (EIC) of budesonide into the aquatic environment is less than 1 ppb. Takeda states that there are no extraordinary circumstances associated with the use of budesonide. The categorical exclusion is therefore granted.

In summary, Dr. Venkateswara Pavuluri has recommended approval of this application from the drug product perspective. See IQA Chapter II, Drug Product for details.

Labeling: Inadequate

Because deficiencies in the application identified by the clinical division that preclude discussion of labeling, the labeling negotiations have not completed in this review cycle. As of this review, the deficiencies delineated in the CMC labeling review has not been satisfactorily resolved. NOTE: Further assessment and internal discussion of the labeling and labels are necessary before communicating final FDA recommended revisions to the Applicant. Refer to IQA Chapter IV Labeling for details.

Manufacturing Integrated Assessment: Adequate

Process:
The proposed drug product is a budesonide oral suspension packaged into unit dose packs (Stick Packs). The batch formula provided is representative of the registration batches and the same as proposed for the commercial drug product.

The manufacturing process includes (b) (4) (b) (4) (b) (4) The OPMA reviewer Dr. Frank Wackes has concluded the overall manufacturing process is adequate.

Facilities:
The drug product manufacturing facility, (b) (4) has been previously utilized in manufacture of a solution product in similar unit dose pocket packs. The OPMA reviewer Dr. Frank Wackes concluded that the DS and DP manufacturers and external testing facilities are adequate based on the review of the compliance history, profile codes and experience in the proposed responsibilities to support this application.

The OPMA reviewer Dr. Frank Wackes has recommended approval for NDA 213976 from the OPMA perspective. See IQA Chapter V Manufacturing Integrated Assessment for details.

Biopharmaceutics: Adequate

The following dissolution method and the acceptance criteria is acceptable as the quality control method for the proposed drug product Budesonide oral suspension.

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	50 rpm
Volume	500 mL

Medium	0.25% SDS in 0.009N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT (b)(4)% (Q) in 10 minutes

The approved dissolution method will provide the discriminating ability towards API particle size distributions.

The Applicant provided comparative dissolution profiles for the drug product Lot MEE or PR170622.001 which was used in the bioavailability study SHP621-101 and manufactured at (b)(4) and the registration lot #911490 manufactured at the proposed commercial site, (b)(4) The provided dissolution profile data indicate that these two lots have similar dissolution profiles. Therefore, the change in the drug product manufacturing site from the clinical drug product manufacturing site, (b)(4) to the proposed commercial manufacturing site (b)(4) is adequately bridged from a Biopharmaceutics perspective.

The biopharmaceutics reviewer Dr. Kaushalkumar Dave reviewed the overall contents related to the biopharmaceutics in this NDA and concluded that the information in NDA 213976 is adequate to support this NDA approval from the biopharmaceutics perspective. See IQA Chapter VI Biopharmaceutics for details.

Note: A non-approvability comment should be included in the "ADDITIONAL COMMENTS" section of the Complete Response Letter. Details see the attachment I "Text for Complete Response Letter".

Microbiology (if applicable): Adequate

Eohilia (budesonide) oral suspension, 2mg/10mL is an aqueous, non-sterile, viscous suspension for oral administration. It is packaged in child-resistant single-dose stick packs. The testing of the (b)(4) assays (b)(4) microbial limits of TAMC and TYMC per USP <61> and E. Coli per USP <62> and BCC per USP <60> are part of the drug product specification. The overall manufacturing and the environmental monitoring, along with appropriate testing, provide assurance of acceptable microbiological quality of the drug product.

The microbiology data during the stability study provided to date is adequate to support the proposed 24 months shelf-life of the drug product when stored at (b)(4) -25°C.

The microbiology reviewer Dr. Yan Zheng has found the information provided in the application adequate to support the approval of this

application from the microbiology perspective. See IQA Chapter VII Microbiology for details.

APPEARS THIS WAY ON ORIGINAL

FACILITY STATUS REPORT AND OVERALL RECOMMENDATION
As of 04/06/2021

APPEARS THIS WAY ON ORIGINAL

Time run: 4/6/2021 5:00:08 PM

Latest Submission Manufacturing Status for NDA-213976-Original-1

Latest Overall Manufacturing Inspection Recommendation
Approve
Completion Date: 3/29/2021
NDA-213976-ORIG-1-AMEND-15

Inspection Requested
0

Inspection Completed
0

Hint: Click Facility ID link to open Facility Program
Click Facility Name to open Facility Status View: Detail

Facility ID	FEI	Facility DUNS	Facility Name	Latest Facility Status /As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason

(b) (4)

Overall Status by Project for NDA-213976-Original-1

Recommendation	Project Name	Completion Date	Submission Status	Submission Status Effective Date
Approve	NDA-213976-ORIG-1-AMEND-15	03/29/2021	Pending	
	NDA-213976-ORIG-1-AMEND-16	03/29/2021	Pending	
No Evaluation Necessary	NDA-213976-ORIG-1-AMEND-14	03/29/2021	Pending	
No Evaluation Necessary	NDA-213976-ORIG-1-AMEND-12	03/29/2021	Pending	
No Evaluation Necessary	NDA-213976-ORIG-1-AMEND-9	03/29/2021	Pending	
No Evaluation Necessary	NDA-213976-ORIG-1-AMEND-8	03/29/2021	Pending	
Approve	NDA-213976-ORIG-1	02/18/2021	Pending	
No Evaluation Necessary	NDA-213976-ORIG-1-PSUB-3	03/29/2021	Presubmission	
No Evaluation Necessary	NDA-213976-ORIG-1-PSUB-2	03/29/2021	Presubmission	
No Evaluation Necessary	NDA-213976-ORIG-1-PSUB-1	03/29/2021	Presubmission	

C. Risk Assessment

Attributes/CQAs	Initial Risk Ranking	Mitigation Strategy	Updated Risk Ranking after Assessment Cycle #1	Lifecycle Considerations/Comments
Identification	L	(b) (4)	L	
Assay	L		L	
Content Uniformity	M		L	
Related Substances (b) (4)	M		L	
Viscosity	M		L	
(b) (4) Assay	L		L	
Dissolution	M		L	
pH	L		L	
(b) (4) Assay	L		L	
Microbial Limits	L		L	

Note: The OPMA review team recommends that, following approval of this NDA, a follow-up evaluation of the drug product manufacturer, (b) (4) be conducted under the CDER OPMA Post-Approval Inspection program in order to confirm the successful performance of the Process Validation and to evaluate the commercial batch history. For details refer to IQA Chapter V Manufacturing Integrated Assessment.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

na

2. Drug Substance Deficiencies

na

3. Drug Product Deficiencies

na

4. Labeling Deficiencies

The labeling negotiations have not completed in this review cycle. The deficiencies delineated in the CMC labeling review have not been conveyed to the Applicant at this time.

5. Manufacturing Deficiencies

na

6. Biopharmaceutics Deficiencies

na

7. Microbiology Deficiencies

na

8. Other Deficiencies (Specify discipline, such as Environmental)

na

Application Technical Lead Name and Date:

Hong Cai, Ph.D. M.Ed.
Application Technical Lead

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate		See IQA Chapter 1, Drug Substance for additional information
	II			Adequate		See IQA Chapter 1, Drug Substance for additional information
	IV			NA		See IQA Drug Product Chapter for additional information
	III			NA		See IQA Drug Product Chapter for additional information

N/A: There is enough data in the application, therefore the DMFs did not need to be reviewed during the current review cycle. Refer to the email communication received from the drug product reviewer Dr. Venkateswara Pavuluri dated 03/29/2021.

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND submissions, associated reviews, and communications	IND 103173	Investigational use of budesonide oral suspension
NDA application(s) as the Listed Drugs	NDA 021324	Entocort EC (budesonide) delayed-release capsules, 3 mg

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	na			
Pharmacology/Toxicology	na			
CDRH-ODE	na			
CDRH-OC	na			
Clinical	na			
Other	na			

ATTACTMENT I: Text for Complete Response Letter

The following non-approvability comment should be included in the "ADDITIONAL COMMENTS" section of the Complete Response Letter. Refer to the email communication from the Biopharmaceutics team lead Dr. Tapash Ghosh on April 6, 2021.

BIOPHARMACEUTICS:

In the current submission, you provided limited dissolution data with the proposed dissolution method collected at the time of batch release. If approval of your proposed product needs manufacturing any new batch to fulfill the CR requirements, provide full-profile dissolution data (n= 12) from that newly manufactured batch collected at the time of batch-release in the next submission. If no new batch manufacturing is required for approval of your product in terms of fulfilling the CR requirements, only upon approval of the proposed drug product, collect full-profile dissolution data (n= 12) for the first six commercial batches at the time of batch-release and provide these data to the FDA in your annual report.

CHAPTERS: Primary Quality Assessment

CHAPTER I: Drug Substance

CHAPTER II: Drug Product

CHAPTER III: Environmental Assessment (see Chapter II)

CHAPTER IV: Labeling

CHAPTER V: Manufacturing Integrated Assessment

CHAPTER VI: Biopharmaceutics

CHAPTER VII: Microbiology

CHAPTER VIII: Additional Quality Disciplines *Not applicable*

65 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: As submitted in eCTD SN 0015, Date: 21-DEC-2020

(b) (4)

[redacted]

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	EOHILIA™	Acceptable per DMEPA assessment.
Established name(s)	Budesonide	Acceptable.
Route(s) of administration	Oral	Acceptable.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral suspension: 2 mg/10 mL	Acceptable.

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet	Not Applicable.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an injectable.	Not Applicable.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) oral, (b) (4) (b) (4)	Not Applicable.

(b) (4)

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Suspension	Acceptable.
Strength(s) in metric system	2mg/ 10 mL	Acceptable.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not a salt	Not Applicable.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	white to yellow, cherry-flavored, (b) (4) viscous suspension	Acceptable.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet	Not Applicable.
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Not an injectable.	Not Applicable.

(b) (4)

[redacted]

Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	EOHILIA	**NOT Acceptable, Revise as EOHILIA (Budesonide oral suspension)**
Dosage form(s) and route(s) of administration	Suspension, Oral	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Not a salt.	Not Applicable.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	acesulfame potassium, Avicel® RC591, ascorbic acid, cherry flavor, citric acid, dextrose, disodium EDTA, glycerin, Magnasweet® 110, maltodextrin, polysorbate 80, potassium sorbate, sodium ascorbate, sodium benzoate, sodium citrate, and purified water.	**Not Acceptable. The use of proprietary names of inactive ingredients is misleading, per 21 CFR 201.10(c). Revise the sentence to include only names of inactive ingredients (including co-processed excipients) listed by USP /NF names in alphabetical order.**
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Not an injectable.	Not Applicable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Alcohol not present.	Not Applicable.
Statement of being sterile (if applicable)	Not a sterile product.	Not Applicable.
Pharmacological/ therapeutic class	(b) (4)	May be changes to Corticosteroid.
Chemical name, structural formula, molecular weight	Included, as reproduced above	Acceptable.

If radioactive, statement of important nuclear characteristics.	Not Radioactive.	Not Applicable.
Other important chemical or physical properties (such as pKa or pH)	No information included.	Acceptable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	Excipients contain no ingredient made from a gluten-containing grain (wheat, barley, or rye).	Acceptable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	Not Applicable.

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Suspension	Acceptable.
Strength(s) in metric system	2 mg/10 mL	Acceptable.
Available units (e.g., bottles of 100 tablets)	60 single-dose stick packs in carton	Acceptable.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	a white to yellow, cherry-flavored, (b) (4) viscous, suspension; NDC 64764-105-60	Acceptable. The NDC number for unit-dose pack may also be included next to its description; NDC 64764-105-60
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not a tablet.	Not Applicable.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not an Injectable.	Not Applicable

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	**Do not freeze.**	Acceptable
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	No desiccant used.	Not Applicable.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store EOHILIA between (b) (4) °C to 25°C ((b) (4) °F to 77°F); (b) (4) (b) (4) Do not freeze.	Acceptable. Revise as: Store EOHILIA between (b) (4) °C to 25°C ((b) (4) °F to 77°F), excursions permitted between (b) (4) and 30°C (b) (4) ° and 86 °F); (b) (4) (b) (4) (b) (4) **Do not freeze**."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	No disclaimers included about latex or synthetic derivative s of natural rubber.	Acceptable.
Include information about child-resistant packaging	child-resistant single-dose stick packs	Acceptable.

1.2.4 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl

alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Takeda Pharmaceuticals America, Inc. Lexington, MA 02421	Acceptable.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): None

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Container / Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Acceptable.
Dosage strength		Acceptable.
Route of administration	For Oral (b) (4) Only	Acceptable.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	Not Applicable
Net contents (e.g. tablet count)	10 mL single-dose stick pack /	Acceptable.
"Rx only" displayed on the principal display	(b) (4)	Acceptable.
NDC number	NDC 64764-105-60	Acceptable.
Lot number and expiration date	(b) (4)	**Not Acceptable.** Leaving blank spaces for Lot number is not acceptable: The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package, per 21 CFR 201.18. Provide an example of lot number and how it is capable of yielding the complete manufacturing history.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store between (b) (4) °C to 25°C (b) (4) °F to 77°F). Do not freeze.	**Acceptable. Revise the statement on container label (if space permits) and carton as: Store between (b) (4) °C to 25°C (b) (4) °F to 77°F), excursions permitted between (b) (4) and 30°C (b) (4) and 86 °F). Do not freeze.**

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not an Injectable.	Not Applicable.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	Container: single-dose stick pack. Carton: 60 single-dose 10 mL stick packs. For Oral (b) (4) Only	Acceptable.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No Alcohol present	Not Applicable.
Bar code	(b) (4)	Acceptable.

Item	Information Provided in the NDA	Assessor's Comments about Container / Carton Labeling
Name of manufacturer/distributor	Dist. by: Takeda Pharmaceuticals America, Inc. Lexington, MA 02421 USA	Acceptable.
Medication Guide (if applicable)	Patient Instructions and IFU included in the carton.	Acceptable.
No text on Ferrule and Cap overseal	Not Applicable.	Not Applicable.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not Applicable.	No USP monograph for Budesonide Oral suspension exists as of this review date.
And others, if space is available	Shake well for at least 10 seconds prior to opening; Keep Out of reach of Children.	Acceptable.

Assessment of Carton and Container Labeling: Inadequate.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information

1. Revise storage statement as "Store EOHILIA between (b) (4) °C to 25°C ((b) (4) °F to 77°F), excursions permitted between (b) (4) 30°C (b) (4) 86 °F); (b) (4) Do not freeze."

Prescribing Information and Carton:

2. The use of proprietary names of inactive ingredients is misleading, per 21 CFR 201.10(c). Revise the sentence in section 11 DESCRIPTION in prescribing Information and on Carton, to include only names of inactive ingredients (including co-processed excipients) listed by USP /NF names in alphabetical order.

Container (Stick pack) and Carton:

3. Revise the statement on container label (if space permits) and carton as: Store between (b)(4)°C to 25°C ((b)(4)°F to 77°F), excursions permitted between (b)(4) 30°C ((b)(4) 86 °F). Do not freeze.
4. Leaving blank spaces for Lot number is not acceptable: The lot number on the label of a drug should be capable of yielding the complete manufacturing history of the package, per 21 CFR 201.18. Provide an example of lot number and how it is capable of yielding the complete manufacturing history.

Overall Assessment and Recommendation: Not APPROVABLE

As of this review, this application is **not deemed ready for approval** in its present form per 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.; 02-MAR-2021

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

Wendy Wilson-Lee, Ph. D.; __ -MAR-2021

Venkateswara Pavuluri

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

Application No: NDA 213976; 505(b)(2)
Drug Product Name/Strengths: Budesonide Oral Suspension; 0.2 mg/ mL (2 mg/ 10 mL)
Route of Administration: Oral
Indication: Treatment of Eosinophilic Esophagitis (EoE), (b) (4) in patients 11 years and older
Applicant Name: Takeda Pharmaceuticals U.S.A. Inc.
Date of Submission: 08/31/2020 (Original)
Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.
Review Recommendation: Adequate

REVIEW SUMMARY

Submission: The proposed drug product, Budesonide Oral Suspension; 2 mg/ 10 mL (designated as BOS by the Applicant during the development), is a viscous suspension intended for oral administration for the treatment of Eosinophilic Esophagitis (EoE), (b) (4) (b) (4), in patients 11 years and older. This NDA is a 505(b)(2) submission which substantially relies on the prior safety and efficacy findings by the Agency for the Listed Drug (LD) Entocort® EC (NDA 021324, Perrigo Pharma).

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) the proposed dissolution method and acceptance criterion, and (2) formulation bridging.

Dissolution Method: The Applicant had initially used a different dissolution method (referred by the Applicant as 'Method A') for quality control (QC) testing of the proposed drug product (Table 3). However, during the development, the Applicant found this method (Method A) to be inadequate due to (b) (4) (b) (4) Therefore, the Applicant developed a new dissolution method (Method B) for QC testing of the proposed drug product and implemented the new dissolution method during the stability testing period. To support this change in the dissolution method during the stability testing period, the Applicant provided comparability study report. The provided data indicate that the change in dissolution method is adequately bridged.

For the proposed QC dissolution method (Method B), the Applicant's proposed use of USP Apparatus 2 for dissolution testing is appropriate as this is a suitable and commonly used apparatus for dissolution testing of liquid/suspension dosage forms. The Applicant has

proposed to use 0.25% SDS in 0.009N HCl as the dissolution medium. The Applicant reported

(b) (4) Based on the provided information/data, the Applicant's selection of the dissolution testing parameters for further testing of the method's discrimination power is appropriate. Also, the Applicant has adequately demonstrated the discriminating ability of the proposed dissolution method towards particle size distribution of the drug substance. Based on the provided data, the proposed dissolution method is deemed adequate for quality control testing of the proposed drug product.

Dissolution Acceptance Criterion: The Applicant's proposed dissolution acceptance criterion of 'Not less than (b) (4)% (Q) at 10 minutes' is adequately selected and supported by the provided dissolution data. Therefore, the proposed dissolution acceptance criterion is deemed adequate for quality control testing of the proposed drug product.

The final and approved dissolution method and agreed-upon acceptance criterion for the quality control of the proposed drug product at batch release and during stability testing are as follows:

FDA approved dissolution method and acceptance criterion for the proposed product

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	50 rpm
Volume	500 mL
Medium	0.25% SDS in 0.009N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 10 minutes

Formulation Bridging: The composition of the proposed drug product was changed during its development. The Applicant performed a comparative BA study (SHP621-101) to generate PK bridging data between all formulations used in clinical studies and the to-be-marketed drug product (SB-10). These data will be reviewed by the Division of Clinical Pharmacology.

There was a drug product manufacturing site change during the development of the proposed product. Drug product Batch Lot number PR170622.001 that was used in the relative bioavailability study SHP621-101 was manufactured at the clinical drug product manufacturing site, (b) (4) whereas the proposed commercial manufacturing site is (b) (4) The Applicant provided dissolution profiles of these batches collected using the proposed dissolution method. The provided dissolution data indicate that these two batches have similar dissolution profiles (Table 5). Based on the provided dissolution data, the change in the drug product manufacturing site is adequately bridged from a Biopharmaceutics perspective.

RECOMMENDATION: From a Biopharmaceutics perspective, NDA 213976 for Budesonide Oral Suspension; 0.2 mg/ mL (2 mg/ 10 mL) is adequate and recommended for approval.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	08/31/2020	Original NDA Submission
0016	12/23/2020	Quality/Response to Information Request
0025	02/05/2020	Quality/Response to Information Request
0033	03/03/20201	Quality/Response to Information Request

BACKGROUND

The proposed drug product, Budesonide Oral Suspension; 2 mg/ 10 mL (BOS) consists of budesonide (a corticosteroid) formulated in a viscous suspension that is designed to (b) (4) (b) (4). The Composition of the proposed drug product is provided in Table 1. (b) (4) (b) (4)

Table 1 Composition of Budesonide Oral Suspension 0.2 mg/mL

Component	Quality Standard	Function	Composition		
			%w/w	mg/mL[b]	mg/unit
Budesonide (b) (4)	USP	Active ingredient	0.017	0.20	2.0
Avicel® RC-591	NF, Ph. Eur	(b) (4)			
Maltodextrin	NF				
Dextrose	USP, Ph. Eur.				
Disodium EDTA	USP, Ph. Eur.				
Citric acid	USP, Ph. Eur.				
Sodium citrate					
Polysorbate 80	NF, Ph. Eur.				
Glycerin	USP, Ph. Eur.				
Sodium Ascorbate	USP, Ph. Eur.				
Ascorbic Acid					
Sodium benzoate	NF, Ph. Eur.				
Potassium sorbate	NF, Ph. Eur.				
Acesulfame potassium	NF, Ph. Eur.				
Magnasweet® 110	Manufacturer's (b) (4) standards				
Cherry flavor	Manufacturer's (b) (4) standards				
Purified Water	USP, Ph. Eur.				
(b) (4)					
Total			100.00	(b) (4)	

The clinical development program to support registration of BOS consists of a completed Phase 1 relative bioavailability study in healthy adults (SHP621-101: 20 to 50 years, inclusive), 2 completed Phase 2 studies in children, adolescents, and adults with EoE (MPI 101-01: 2 to 18 years, inclusive; MPI 101-06: 11 to 40 years, inclusive), and 2 completed Phase 3 studies in adolescents and adults with EoE (SHP621-301 and SHP621-302: 11 to 55 years, inclusive). In addition, there was an ongoing open-label Phase 3 study in adolescents and adults with EoE (SHP621-303) at the time of the NDA submission.

The composition of the proposed drug product was changed during its development. The Applicant performed a comparative BA study (SHP621-101) to generate PK bridging data between all formulations used in clinical studies and the to-be-marketed drug product (SB-10). These data will be reviewed by the Division of Clinical Pharmacology. There was a drug product manufacturing site change during the development of the proposed product. The Applicant provided dissolution data to support this change.

The Biopharmaceutics review is focused on the evaluation of the 1) proposed dissolution method and acceptance criteria, and (2) formulation bridging, as presented below.

Dissolution Method Development

The Applicant's proposed dissolution method and acceptance criterion are as follow:

Table 2: Applicant's proposed dissolution method and acceptance criterion

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	50 rpm
Volume	500 mL
Medium	0.25% SDS in 0.009N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 10 minutes

Drug Solubility: The Applicant's provided solubility data (Table 3) for budesonide indicate that it is poorly soluble across the physiological pH range. Therefore, the Applicant investigated the solubility in the presence of sodium dodecyl sulfate (SDS).

Table 3: Solubility of budesonide in various media (average of n=3; mg/mL)

% SDS (w/v)	0.1 N HCl	50 mM Sodium Chloride[b]	100 mM Sodium Citrate		50 mM Sodium Phosphate	
	pH 1	pH 2	pH 3	pH 4.6	pH 6	pH 7
0.0	0.003	0.005	0.005	0.002	0.003	0.002
0.05	0.025	0.021	0.017	0.037	0.013	0.023
0.1	0.065	0.074	0.069	0.096	0.074	0.084
0.2	0.199[a]	0.209	0.185	0.191	0.192	0.199
0.3		0.293	0.261	0.287	0.275	0.304
0.4	0.322	0.391	0.371	0.388	0.415	0.337

[a] This concentration was tested at 0.25% SDS (w/v)
[b] pH adjusted through addition of HCl

Dissolution Testing Conditions/Parameters: For selection of the dissolution testing conditions, the Applicant performed several studies as described below.

For selection of the dissolution medium, the Applicant considered (b) (4) (b) (4) However, the Applicant selected Apparatus 2 for dissolution testing of suspensions.

For selection of the dissolution medium, the Applicant preferred (b) (4)
(b) (4)
(b) (4) as shown in Figure 1 for dissolution Method A (Methods A and B discussed later).

Figure 1: Representative (b) (4) of BOS in the Dissolution Media per Dissolution Method A and Method B

(b) (4)

(b) (4)

As a result, 0.009N HCl media with 0.25% w/v SDS was found to provide (b) (4)
(b) (4) of BOS as illustrated by Figure 1. Based on this study, the Applicant selected 0.25% SDS in 0.009N HCl as the medium for dissolution testing of the proposed drug product.

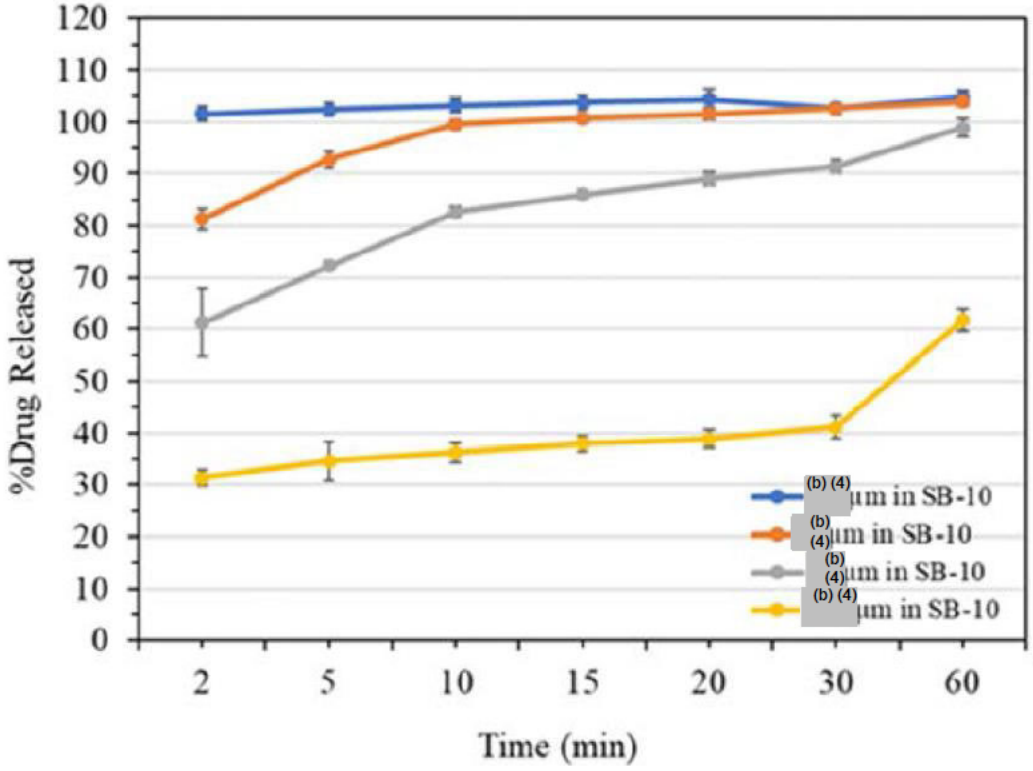
For selection of paddle speed, (b) (4)
(b) (4)

(b) (4) At 50 rpm in 0.009N HCl with 0.25% w/v SDS, the Applicant found the drug release to be acceptable. Based on the above studies/data, the Applicant selected the proposed dissolution method and investigated its discriminating ability.

Testing of the Discrimination Power of the Dissolution Method

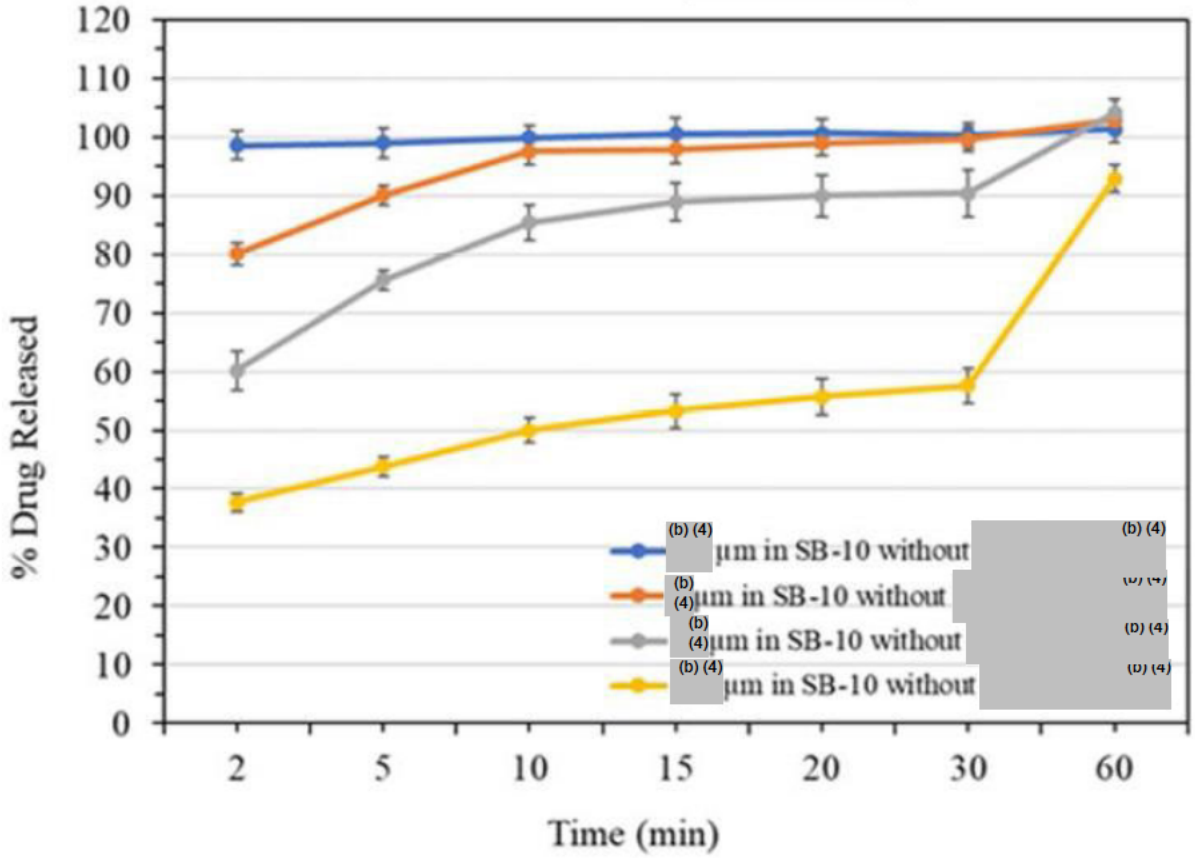
The Applicant investigated the discriminating ability of the proposed dissolution Method against varying API particle sizes. For this, BOS formulations were prepared with VMDs at (b) (4) and their drug release profiles were determined. Based on these study results (Figure 3), the Applicant reported that the proposed dissolution method was able to provide robust discrimination across all the selected particle sizes.

Figure 3: Dissolution Profiles (n=6) of Budesonide Oral Suspension with Four Particle Sizes of API in SB-10 Formulation Placebo per Method B



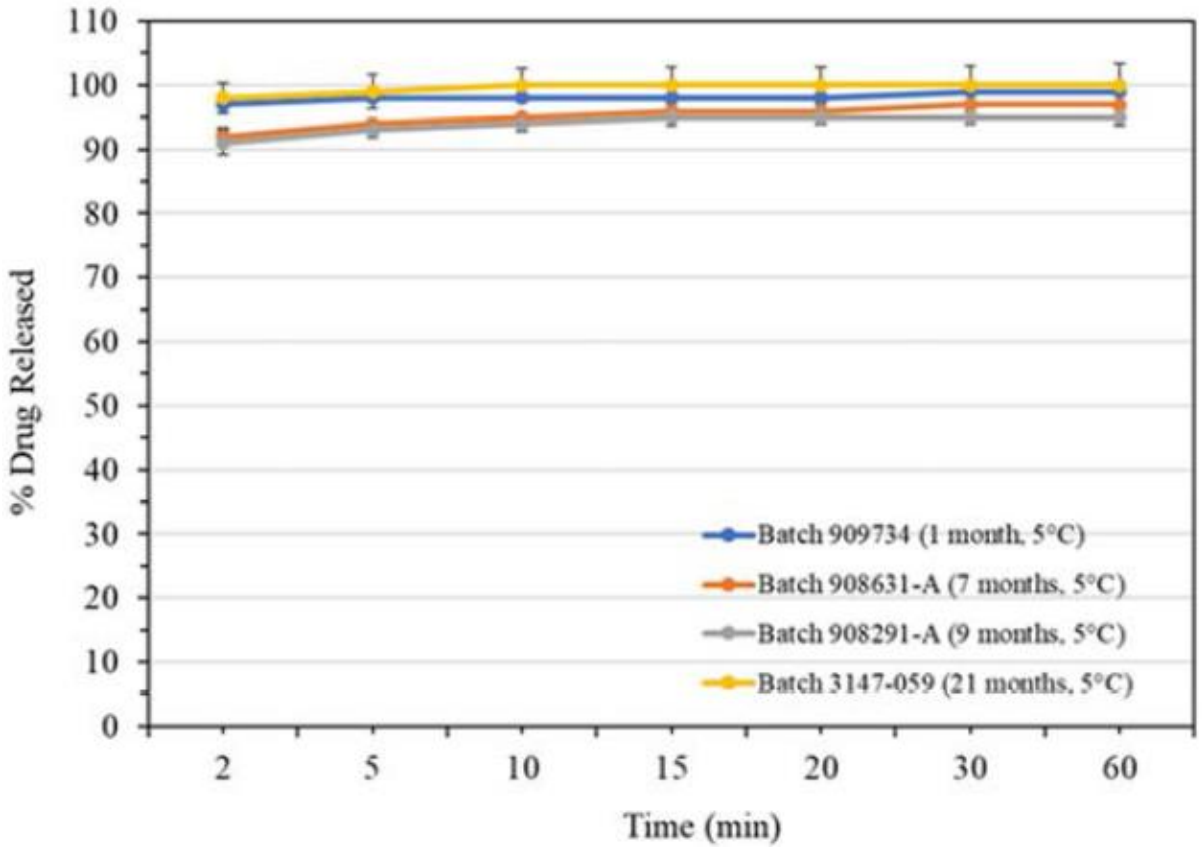
As per the Applicant, BOS is a viscous suspension with thixotropic properties and these characteristics are attributed to the viscosity (b) (4) (b) (4) in the product. To understand if the discriminatory power of the dissolution method would depend on (b) (4) the Applicant prepared BOS formulations without (b) (4) and using varying VMDs at (b) (4) drug release profiles were determined using the proposed dissolution method. The collected dissolution profiles are shown in Figure 4.

Figure 4. Dissolution Profiles (n=6) of BOS with Four Particle Sizes of API in SB-10 Formulation Placebo without [redacted]



The Applicant studied the repeatability of the dissolution method by comparing the release profiles of various batches as shown in Figure 5 at various stability time points (ranging from 1 to 21 months at 5°C storage condition).

Figure 5. Repeatability for Dissolution Method B across Multiple Batches at Various Stability Timepoints (n=6)



Based on the above studies, the Applicant selected the proposed dissolution method for QC testing of the proposed drug product.

Reviewer's Assessment:

The proposed drug product is complex in nature as it employs (b) (4) . The Applicant's proposed use of USP Apparatus 2 for dissolution testing is appropriate as this is a suitable and commonly used apparatus for dissolution testing of liquid/suspension dosage forms. The Applicant has proposed to use 0.25% SDS in 0.009N HCl as the dissolution medium. The Applicant reported that budesonide is (b) (4)

(b) (4)

(b) (4)

Based on the provided information/data, the Applicant's selection of the dissolution testing parameters for further testing of the method's discrimination power is appropriate.

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(b) (4)

Discriminating Ability of the Dissolution Method

For testing the discriminating ability of the proposed method, the Applicant prepared BOS formulations with different VMDs, as shown in Figure 3. The provided mean dissolution data indicate that the dissolution profiles of the BOS prepared with VMD of (b) (4) µm and (b) (4) µm are different from the batches prepared with VMD of (b) (4) µm and (b) (4) µm. However, the dissolution profile of the batch prepared with VMD of (b) (4) µm does not differ significantly from the batch with VMD of (b) (4) µm. As per the Applicant, the proposed particle size specifications for the drug substance are as follows:

≤ (b) (4) µm - ≥ (b) (4) %

≤ (b) (4) µm - ≥ (b) (4) %

≤ (b) (4) µm - ≥ (b) (4) %

Based on the above specification, the drug products prepared with VMDs of (b) (4) µm, (b) (4) µm and (b) (4) µm are out of the specification range and hence should ideally fail in the dissolution test. However, the dissolution method can be discriminating towards these bathes only if the dissolution acceptance criterion is appropriately selected. Based on the provided information/data, the proposed dissolution method is deemed adequate for QC testing of the proposed drug product; however, it is important that the dissolution acceptance criterion be selected adequately to maintain the discriminating ability of the dissolution method towards API particle size distribution.

Dissolution Method Change During Product Development

The Applicant had initially used a different dissolution method (referred by the Applicant as 'Method A') for quality control (QC) testing of the proposed drug product (Table 3). However, during the development, the Applicant found this method (Method A) to be inadequate due to

(b) (4)

which led to (b) (4) as representative examples shown in Figure 8 for three registration batches at release.

Figure 8. Dissolution Profiles of Three Registration Batches of BOS Stick Packs per Dissolution Method A

Therefore, the Applicant developed a new dissolution method (Method B; Table 4) for QC testing of the proposed drug product and implemented the new dissolution method during the stability testing period. Due to this change, for Primary Stability Batches 908507 and 908631, the 0, 1, 3, 6, 9 and 12 months data were collected with 'Method A' and 18, 24, 30, 36, 42 and 48 months data were collected with 'Method B', and for the Primary Stability Batch 909734, the 0, 1, 3 and 6 months data were collected with 'Method A' and 9, 12, 18, 24, 30, 36, 42 and 48 months data were collected with 'Method B'. To support this change in the dissolution method during the stability testing period, the Applicant provided comparability study report in module 3.2.P.5.4 of the submission.

Table 4: Comparison of dissolution Method A and Method B

	Method A	**Method B**
Apparatus	USP Apparatus 2	USP Apparatus 2
Spindle Speed	(b) (4) rpm	50 rpm±2%
Medium	0.25% sodium dodecyl sulfate (SDS) in (b) (4) N HCl	0.25% sodium dodecyl sulfate (SDS) in 0.009N HCl
Dissolution Volume	500 mL + sample volume	500 mL + sample volume
Temperature	37.0°C±0.5°C	37.0°C±0.5°C
Sampling Times	(b) (4)	2, 5, 10, 15, 20, and 30 minutes (and infinity pull at 60 minutes)
Infinity Pull	250 rpm for 30 minutes	250 rpm for 30 minutes
Sample Pull Volume	10 mL	10 mL

The Applicant performed a method comparability bridging study to statistically evaluate precision for both dissolution Methods A and B. The study design is outlined in Table 5 with 12 replicates prepared for each sampling point at each testing interval. Three registration BOS stick pack batches were included in the study. Three clinical batches (MB-9 formulation) were also evaluated. The dissolution profiles per the two dissolution methods for the registration stick pack batches and clinical batches (MB-9 formulation) are shown in Figure 9 and Figure 10, respectively.

Table 5. BOS Batches Tested in the Bridging Study via Both Dissolution Methods A and Method B

Batch#	Formulation	Packaging	Storage Conditions	Stability Study Start Date	Bridging Study Start Date	Bridging Study Time Intervals[a] (weeks)	Sample Age[b] (months)
909734	SB-10	Stick pack	5°C	Oct 2019	Feb-2020	0, 4, 8, 12	4, 5, 6, 7
908631-A	SB-10	Stick pack	5°C	Jun 2019	Feb-2020		8, 9, 10, 11
	SB-10	Stick pack	25°C/60%RH	N/A	Feb-2020		0, 1, 2, 3
908507-A	SB-10	Stick pack	5°C	Apr 2019	Feb-2020		10, 11, 12, 13
PEB-C	MB-9	(b) (4)	5°C	Jun 2019	Jan-2020		7, 8, 9, 10
PAD-C	MB-9		5°C	Mar 2019	Jan-2020		10, 11, 12, 13
NER-C	MB-9		5°C	Jan 2019	Jan-2020		12, 13, 14, 15
	MB-9		25°C/60%RH	N/A	Jan-2020		0, 1, 2, 3

N/A=not applicable

[a] Time intervals for the bridging study after BOS samples were relocated into storage chambers to initiate the tests.

[b] Actual stability sample age corresponding to their individual time intervals in the bridging study.

Figure 9. Dissolution Profiles for Stick Pack SB-10 Formulation Registration Batches per Dissolution Methods A and B

(b) (4)

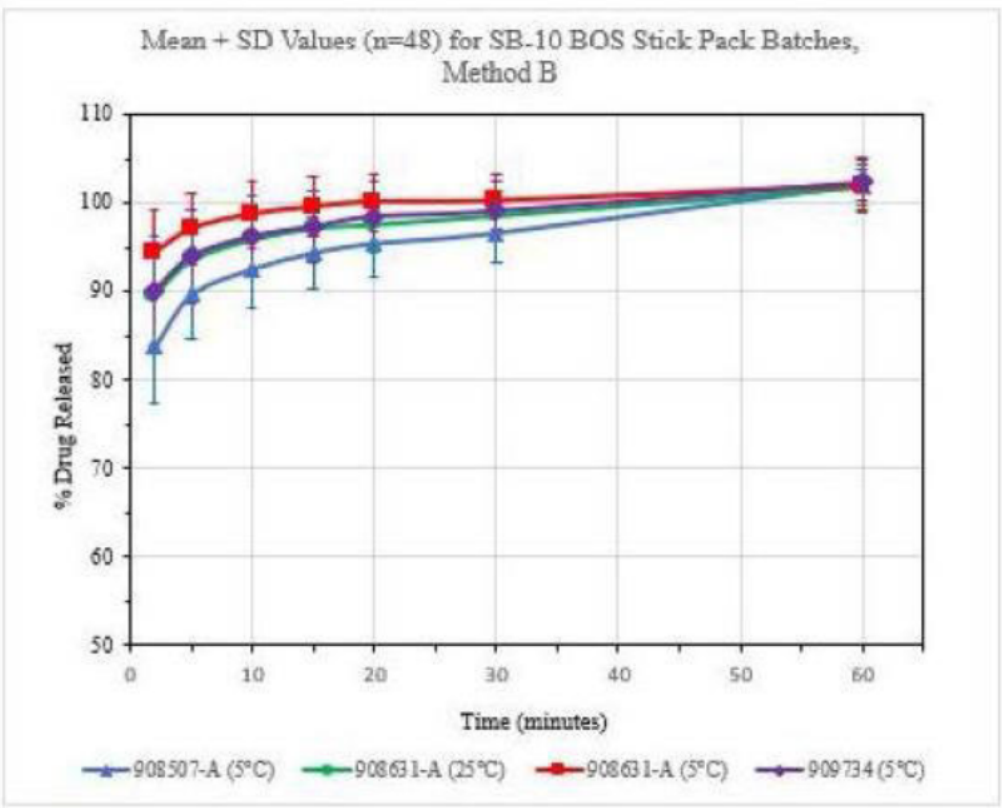
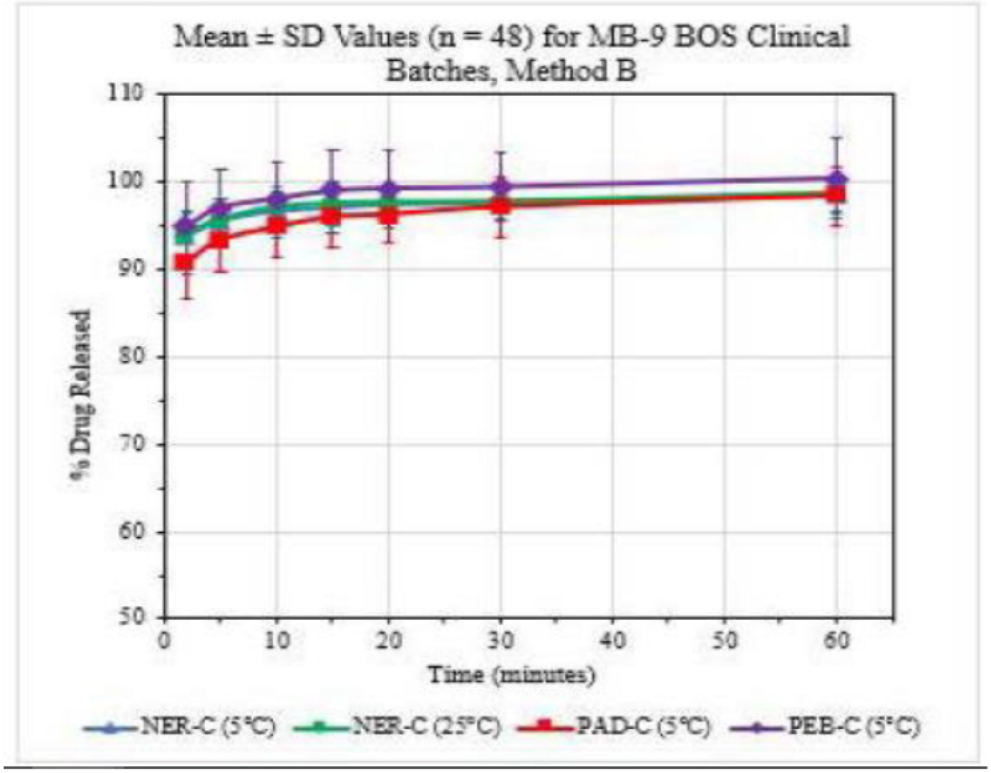


Figure 10. Dissolution Profile for MB-9 Formulation Clinical Batches per Dissolution Methods A and B

(b) (4)



For method precision comparison, the Applicant calculated 90% CI for the ratio of SD (standard deviation) of percent dissolved values for dissolution Method B over Method A using two-sided F-tests and concluded that the Method B was significantly more precise than Method A (Table 6).

Table 6. Standard Deviation Ratios for First Timepoint with at Least One Vessel with ≥85% Dissolved for Dissolution Methods A and B

Package	Batch# (temp.)	Method B			Method A			SD Ratio	90% CI for Ratio of SDs	
		Time point (minute)	Var[a]	SD	Time point (minute)	Var[a]	SD		Lower	Upper
(b) (4)	NER-C (25°C)	2	6.49	2.55	(b) (4)					
	NER-C (5°C)	2	8.05	2.84						
	PAD-C (5°C)	2	15.47	3.93						
	PEB-C (5°C)	2	27.77	5.27						
Stick-pack	908507-A (5°C)	2	41.80	6.47						
	908631-A (25°C)	2	33.27	5.77						
	908631-A (5°C)	2	22.66	4.76						
	909734 (5°C)	2	37.57	6.13						

[a] The variance of dissolution (n=48) calculated for the first timepoint with at least one vessel having percent dissolved ≥ (b) (4)% within each batch and method.

Reviewer's Assessment

The Applicant's provided dissolution data indicate that method A is not suitable for dissolution testing of the proposed drug product (b) (4) (b) (4) The proposed dissolution method (Method B) is not very different from Method A in terms of dissolution testing parameters. These two methods vary only in the HCl concentration (method A used (b) (4) N HCl with 0.25% SDS while method B uses 0.009N HCl with 0.25% SDS) and the paddle speed (method A used (b) (4) rpm while method B uses 50 rpm). Since the proposed dissolution method offers (b) (4) during dissolution testing which leads to (b) (4), and it is discriminating, the Applicant's approach of using the dissolution method B for QC testing of the proposed drug product is reasonable. However, the Applicant did not provide batch-release data for the clinical and registration batches collected at the time of batch release with the proposed dissolution method. The provided dissolution data for comparability testing are collected during the stability testing period. Therefore, the Applicant was recommended via IR dated 02/22/2021[2] to collect full profile data for the first 6 commercial batches and submit to the FDA for review in the future submission. In response (dated 03/03/2021[2]), the Applicant agreed to provide these data in the future submission. The Applicant's response is adequate.

[2] \\CDSESUB1\evsprod\nda213976\0033\m1\us\quality-information-amendment.pdf

Dissolution Acceptance Criterion

As per the current practice at the Division of Biopharmaceutics, the dissolution acceptance criterion is set based on dissolution profiles of the clinical and registration batches at the time of release. In the original submission, the full-profile dissolution data for these batches were not provided. Therefore, the Applicant was recommended (via an IR sent on 12/08/2020[3]) to provide these data. In response (dated 12/23/2020[3]), the Applicant provided full-profile dissolution data for the clinical and registration batches (Appendix 1).

The data from the studies testing the discriminating ability of the proposed method indicate that the proposed dissolution method will be discriminating if the dissolution acceptance criterion is appropriately selected. The Applicant's currently proposed dissolution acceptance criterion of 'Not less than (b) (4)% (Q) at 10 minutes' is appropriately selected and hence deemed adequate.

The FDA's approved dissolution method and acceptance criterion for the proposed product are described in Table 7.

Table 7: FDA approved dissolution method and acceptance criterion for the proposed drug product

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	50 rpm
Volume	500 mL
Medium	0.25% SDS in 0.009N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criteria	NLT (b) (4)% (Q) in 10 minutes

Formulation Bridging

The composition of the proposed drug product was changed during its development. Therefore, the Applicant performed a comparative bioavailability study (SHP621-101) to generate PK bridging data from all the formulations used in clinical studies and the to-be-marketed drug product (SB-10). The data from this study will be reviewed by the Clinical Pharmacology Review Team. The Clinical study report for the Study SHP621-101 indicate that Batch PR170622.001 of the TBM formulation (SB-10; mentioned as 'MB-9 formulation with (b) (4) in the clinical report) was used in this study. This Reviewer could not locate the information for manufacturing site for this batch. However, the Applicant has stated in the submission that the drug product batches used in the study SHP621-101 were manufactured at (b) (4) while the manufacturing site for the to-be-marketed

[3] \\CDSESUB1\evsprod\nda213976\0016\m1\us\cover-letter.pdf

drug product is [redacted] Therefore, the following IR was sent to the Applicant on 02/22/2021:

- Provide batch analysis results for the drug product Batch Lot number PR170622.001 that was used in the relative bioavailability study SHP621-101. You should also include the following CMC information of the drug product lot PR170622.001: full-profile dissolution data, the drug substance batch and source, the manufacturing date, batch scale and the manufacturing site.

- Confirm that the formulation of the drug product lot PR 170622.001 is identical to the proposed commercial formulation and the manufacturing site is the same as the proposed commercial site.

- In case the drug product manufacturing site for the aforementioned drug product lot is different from the proposed commercial drug product manufacturing site, [redacted], for NDA 213976, provide appropriate bridging comparison analysis between the drug products from different manufacturing sites. Similarly, if the drug product composition/formulation for the aforementioned drug product lot is different from the composition/formulation of the proposed commercial drug product for NDA 213976, provide appropriate bridging comparison analysis between these drug products.

In response (dated 03/03/2021), the Applicant stated that the drug product batch utilized for relative bioavailability study SHP621-101 is the same as bulk drug product lot MEE. The lot number MEE was assigned by clinical drug product manufacturing site, [redacted] Upon labelling for clinical studies, the lot number PR170622.001 was assigned to the finished drug product. The Applicant provided the requested information and data for this batch. In the response, the Applicant confirmed that the formulation of drug product lot PR 170622.001 (which is same as bulk lot number MEE) is identical to the commercial formulation (SB-10). However, lot PR170622.001 was manufactured at the clinical drug product manufacturing site, [redacted] whereas the proposed commercial manufacturing site is [redacted] The Applicant provided a comparative bridging analysis of batch #MEE to that of a proposed commercial drug product batch (#911490). The batch #911490 is one of the registration stability batches that were manufactured at [redacted] The Applicant provided a comparison of the manufacturing process equipment and process parameters employed for these two batches. These data will be reviewed by the process review team. The Applicant provided dissolution profiles of these batches collected using the proposed dissolution method (Method B). The provided dissolution data indicate that these two batches have similar dissolution profiles (Table 8).

Table 8. Comparison of Dissolution Profiles of the BOS batch #MEE and #911490 (per Dissolution method B)

Attribute		Acceptance Criteria	Batch #MEE Stability Samples at 5°C for 26 months	Batch #911490 Initial Stability Sample
	Time (min)		**% drug released (mean)**	
Dissolution (per Method B)	2	Q= (b) (4)% at 10min	89	93
	5		91	96
	10		92	97
	15		91	98
	20		93	98
	30		93	99
	Infinity		93	99

Based on the provided dissolution data, the change in the drug product manufacturing site is adequately bridged from a Biopharmaceutics perspective.

Appendix 1

Dissolution Data of BOS Batches at Initial Timepoints per Method B

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
NER-C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	91	93	95	95	96	96	98

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
PAD-C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	91	93	94	95	96	96	96

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
PEB-C	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	89	92	94	95	95	96	97

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
908507-A	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	83	88	90	92	93	94	98

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
908631-A	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	94	96	98	99	99	100	101

Batch No.	Vessel No.	Dissoved% at Initial Timepoint from Bridging Studies (min)						
		2	5	10	15	20	30	Infinity
909734	1	(b) (4)						
	2							
	3							
	4							
	5							
	6							
	7							
	8							
	9							
	10							
	11							
	12							
	Mean	95	98	100	101	101	102	103

Kaushalkumar Dave

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213976
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Budesonide (Eohilia)/ 0.2 mg/mL
Route of Administration	Oral suspension
Applicant Name	Takeda Pharmaceuticals U.S.A. Inc.
Therapeutic Classification/ OND Division	OND/OII/DG
Manufacturing Site	(b) (4)
Method of Sterilization	N/A for non-sterile products

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
ORIG-1, new NDA	10/15/2020
Amendment	11/12/2020
Amendment	12/16/2020
Amendment	12/21/2020

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is eCTD submission. Submission dated 11/12/2020 is provided with updated labeling information. Submission dated 12/16/2020 is provided in response to the Agency's information request dated 12/01/2020. Submission dated 12/21/2020 is provided with updated P 5.2 and P.8 section for BCC testing.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None.

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The proposed product (EOHILIA, 2 mg/10 mL budesonide oral suspension) is a single-dose, aqueous, non-sterile, viscous suspension for oral administration. It is packaged in child-resistant single-dose stick packs (2 mg/unit).

Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Yan Zheng

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