CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210745Orig1s000
210745Orig2s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 210475 (Resubmission) Integrated Quality Assessment

RECOMMENDATION

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

NDA 210475
Assessment #1

Drug Product Name	apremilast extended-release tablet
Dosage Form	Tablet
Strength	75 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Amgen, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original resubmission (SD-17)	30-Oct-2024	All
Amendment (SD-19)	20-Dec-2024	Manufacturing/Facilities
Amendment (SD-23)	11-Mar-2025	Biopharmaceutics
Amendment (SD-24)	15-Apr-2025	Manufacturing/Facilities
Amendment (SD-26)	30-Apr-2025	Manufacturing/Facilities
Amendment (SD-28)	25-Jun-2025	Biopharmaceutics
Amendment (SD-29)	09-Jul-2025	Manufacturing/Facilities
Amendment (SD-30)	14-Jul-2025	Manufacturing/Facilities

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	N/A	
Drug Product	Hitesh Shroff	Craig M. Bertha
Manufacturing/Facilities	Miral Patel	Shu-Wei Yang
Microbiology	N/A	
Biopharmaceutics	Hansong Chen	Ta-Chen Wu
Labeling	Hitesh Shroff	Julia Pinto
Regulatory Business Process Manager	Stephanie Ngan	

Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	Hitesh Shroff	Craig M. Bertha

Table of Content Hyperlinks

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type III		(b) (4)	Active since 11/15/1971	N/A	LOA: July 29, 2024 Not reviewed because Necessary information provided in the NDA.
	Type III			Active since 02/15/1977	N/A	LOA: September 4, 2024 Not reviewed because Necessary information provided in the NDA.
	Type III			Active since 04/09/1980	N/A	LOA: June 22, 2017 Not reviewed because Necessary information provided in the NDA.
	Type III			Active since 11/17/1986	N/A	LOA: March 1, 2023 Not reviewed because Necessary information provided in the NDA.
	Type III			Active since 12/20/2006	N/A	LOA: July 29, 2024 Not reviewed because Necessary information provided in the NDA.
	Type III			Active since 02/25/1998	N/A	LOA: July 29, 2024 Not reviewed because Necessary information in the NDA.

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

Document	Application Number	Description
IND	70270	tablet for psoriasis
IND	121919	capsule for psoriatic arthritis
IND	101761	capsule for psoriatic arthritis and Behcet disease
NDA	205437	tablet for psoriatic arthritis
NDA	206088	tablet for plaque psoriasis

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Office of Pharmaceutical Quality

New Drug Application (NDA) 210745 (Resubmission) Integrated Quality Assessment

NDA Executive Summary

1. Application/Product Information

NDA Number	210745
Applicant Name	Amgen, Inc.
Drug Product Name	Otezla XR (apremilast) extended-release tablets
Dosage Form	Tablet, extended release
Proposed Strength(s)	75 mg
NDA Classification	Type 3 - New Dosage Form
Route of Administration	Oral
Maximum Daily Dose	75 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For treatment of adults with psoriatic arthritis and patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Drug Product Description	Apremilast is a phosphodiesterase 4 inhibitor used to treat active psoriatic arthritis and plaque psoriasis. Immediate release tablets of 10, 20, and 30 mg strengths from Celgene, are already approved. This NDA proposes an extended-release tablet (b) (4) for once-daily dosing. (b) (4) (b) (4)

	(b) (4)		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	
	Drug Product	Hitesh Shroff	Craig M. Bertha
	Manufacturing	Miral Patel	Shu-Wei Yang
	Biopharmaceutics	Hansong Chen	Ta-Chen Wu
	Microbiology	N/A	
	Labeling	Hitesh Shroff	Julia Pinto
	Other (specify)	N/A	
	RBPM	Stephanie Ngan	
	ATL	Craig M. Bertha	
Consults	N/A		

2. Final Overall Recommendation - *Adequate*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant has provided additional information in response to Agency information requests and there are no unresolved CMC-related issues remaining. Therefore, approval of the application is recommended from the CMC perspective.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	**N/A**
Drug Product	-	**Adequate**
Quality Labeling	-	**Pending**[1]
Manufacturing	-	**Adequate**
Biopharmaceutics	-	**Adequate**
Microbiology	-	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

Application Technical Lead Name and Date:

Craig M. Bertha, CMC Reviewer, 22-Jul-2025

[1]The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

Final Risk Assessment for NDA 210745 (RESUB-17)

DP attribute/ CQA	Factors that may impact the CQA	O[2]	S[1, 3]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments and/or Lifecycle considerations
Appearance	(b) (4)	2	1	2	4			
Identification		1	3	1	3	(b) (4)		
Assay, degradation products		3	3	2	18			
Uniformity of dosage units		3	3	3	27	(b) (4)		

[2] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[3] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

						(b) (4)		
(b) (4)	(b) (4)	2	3	2	12			
Drug Release or Dissolution		2	3	5	30		2x3x2=12	(b) (4)

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

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 210745 resub
Assessment Cycle Number	02
Drug Product Name/ Strength	OTEZLA XR™ (apremilast) extended-release tablets, 75 mg
Route of Administration	Oral
Applicant Name	Amgen Inc. (Amgen)
Therapeutic Classification/ OND Division	Phosphodiesterase 4 (PDE4) inhibitors / OND/OII/DRTM
LD/RS Number	NDA 205437
Proposed Indication	For the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Assessment Recommendation: **Adequate**

Assessment Summary:

On October 30, 2024, Amgen resubmitted this NDA to seek approval through the 505(b)(2) regulatory pathway relying on FDA's efficacy and safety findings of Listed Drug (LD) OTEZLA® immediate-release (IR) tablets 10 mg, 20 mg, and 30 mg (NDA 205437). The proposed indication is for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Note that Celgene Corporation developed OTEZLA XR™ (apremilast) extended-release tablets, 75 mg and submitted the original NDA 210745 on December 15, 2017, but withdrew it on August 17, 2018, before FDA action. NDA 210745 ownership transferred from Celgene to Amgen on June 21, 2022.

The key findings of Biopharmaceutics assessment are summarized as follows:

I. Proposed dissolution method and acceptance criteria:

The Applicant's proposed dissolution method [USP apparatus II (paddle) with sinkers at 75 rpm; 900 mL of 0.5% Tween 80 in sodium acetate buffer pH 5.5 at 37 °C] is acceptable. The proposed dissolution method was demonstrated to be discriminatory towards changes in the amount of (b) (4)

The final agreed-upon dissolution acceptance criteria for batch release and stability testing were set based on the provided dissolution profile data of clinical and registration batches and demonstration of the discriminating power of the proposed dissolution method:

2 h: NMT (b)(4)%
8 h: (b)(4)%
24 h: NLT (b)(4)%

II. Extended-Release (ER) claim:

The "Extended-Release" claim for the proposed OTEZLA XR™ (apremilast) extended-release tablets, 75 mg is supported by the following information and data:

- ER characteristics of the proposed OTEZLA XR™ (apremilast) extended-release tablets, 75 mg as demonstrated by comparison its plasma concentration-time profile (once-daily or QD) with the LD (i.e., OTEZLA® immediate-release (IR) tablets, BID, NDA 205437), with less peak/trough fluctuation.
- The proposed drug product's steady-state performance is equivalent to a currently marketed immediate release drug product (i.e., OTEZLA® immediate-release (IR) tablets, BID, NDA 205437), per the pivotal relative bioavailability/bioequivalence (BA/BE) study results.
- The bioavailability profile established for the proposed drug product rules out the occurrence of dose-dumping and hence quality concerns for the proposed drug product.
- The proposed drug product's formulation provides consistent pharmacokinetic performance between individual dosage units, including acceptable variability as reported in the relative BA/BE study.
- As supportive evidence for drug release as designed, the extended-release characteristics of the proposed drug product were also demonstrated in in-vitro test conditions.

III. In vitro alcohol-induced dose-dumping potential:

Results from the in vitro alcohol-induced dose-dumping study show there is no alcohol-induced dose-dumping observed in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with alcohol, indicating that the presence of alcohol would have insignificant impact on drug release from the proposed ER drug product. Note that the mean % drug releases up to 2 hours are similar. The effect of 40% alcohol, 8-14% increases as seen in cumulative amount overtime, did not become apparent until after 10-12 hours. Results are deemed insignificant from a drug-release.

There is no alcohol-induced dose-dumping observed in 0.1 N HCl with alcohol up to 2 hours, indicating that the presence of alcohol would have insignificant impact on drug release from the proposed ER drug product in the relevant physiologic condition with consumption of alcohol or alcohol beverages. The effect of 40% alcohol or noticeable separation in drug release profile, as seen in cumulative amount overtime, did not become apparent until after 10-12 hours encompassing the small intestine transit time, and reached approximately 31% higher vs. control. Note that all lower % alcohol concentrations (up to 20%) showed similar release profile, for which this Reviewer considered more clinically relevant.

The Applicant did not propose labeling instruction regarding clinical consequences with patient consumption of alcohol/alcoholic beverages while taking the proposed ER drug product. The Biopharmaceutics findings were communicated for proper labeling recommendations.

IV. Risk assessment:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	High	The proposed drug product is Extended-Release Tablets	Low	The dissolution method is able to discriminate changes in the amount of (b) (4)

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 210745 for OTEZLA XR™ (apremilast) extended-release tablets, 75 mg, is ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

Apparatus	II (Paddle) with sinker
Speed	75 rpm
Medium	0.5 % Tween 80 in sodium acetate buffer pH 5.5
Medium volume	900 mL
Temperature	37 °C
Sampling times	2, 6, 8, 10, 14, 16, 18, and 24 hours
Acceptance criteria	2 h: NMT (b) (4)% 8 h: (b) (4)% 24 h: NLT (b) (4)%

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Sequence 00017 /Resubmission submission	10/30/2024
Sequence 0023 /Response to Biopharmaceutics IR 1	3/1/2025
Sequence 0028 /Response to Biopharmaceutics IR 2	6/25/2025

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

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

B.1 BCS DESIGNATION

Assessment:
Per NDA 205437 Biopharmaceutics review, apremilast is a BCS Class IV drug, which has low solubility and low permeability.

Solubility:
The solubility data in pH 1 – 8 provided in NDA 205437 submission (Amgen is also the owner of NDA 205437) show that apremilast is poorly soluble based on the highest single dose (30 mg), per BCS criteria. (b) (4)

Table 1. Aqueous solubility of apremilast in different pHs ((b) (4)

pH	1	2	3	4	5	6	7	8
Solubility (µg/mL)	13.05	14.54	14.19	13.01	11.37	11.01	10.81	11.62

Permeability: Per NDA 205437 Biopharmaceutics review, the determined intrinsic apparent permeability value for apremilast across porcine kidney epithelial cell (LLC-PK1) monolayers was 21 x 10^{-6} cm/sec. The permeability study protocol/details were not submitted in the NDA 205437 submission. Therefore, the data were not sufficient to permit an independent review of the proposed claim of low permeability.

Dissolution: N/A (see B.2 section)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate.

1. Drug product

The drug product consists of apremilast 75 mg extended-release tablets manufactured using (b) (4)). (b) (4)

(b) (4)

(b) (4)

(b) (4)

Table 3. Composition of Apremilast (b) (4), 75 mg

Component	Function	Quality Standard	mg/tablet
(b) (4)			
Apremilast	Active	In-house	75.0
Hypromellose (b) (4)	(b) (4)	NF	(b) (4)
Polyethylene oxide		NF	
Mannitol		USP	
Magnesium stearate		NF	
(b) (4)			
Colloidal silicon dioxide		NF	
(b) (4		USP	
		NF	
		NF	
Microcrystalline cellulose		NF	
Sodium chloride		USP	
Iron oxide red		NF	
(b) (4)		NF	
Cellulose acetate		NF	
Polyethylene glycol		NF	
(b) (4)		NF	
		USP	
		In-house	
		USP	
Total weight of final film coated tablets			

[a] (b) (4)

2. Dissolution method

1) The proposed dissolution method

The Applicant proposed a dissolution method using USP Apparatus II (Paddle) with sinker (Table 4) and a full dissolution method development report justifying the selection of the method's parameters.

Table 4. The proposed dissolution method

Apparatus	II (Paddle) with sinker
Speed	75 rpm
Medium	0.5 % Tween 80 in sodium acetate buffer pH 5.5
Medium volume	900 mL
Temperature	37 °C
Sampling times	2, 6, 8, 10, 14, 16, 18, and 24 hours

2) Selection of apparatus and agitation speed:

(b) (4)

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

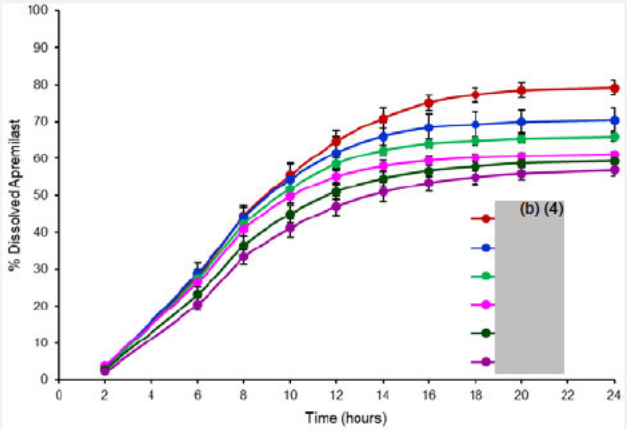
(b) (4)

3) Discriminating power of dissolution method

Effect of different (b) (4) in apremilast 75 mg (b) (4) tablets on dissolution:

The Applicant intentionally manufactured Apremilast,75 mg (b) (4) tablets with (b) (4) and compared their dissolution profiles with that of the reference batch (b) (4). As illustrated in Figure 7, the drug release rate decreases when (b) (4).

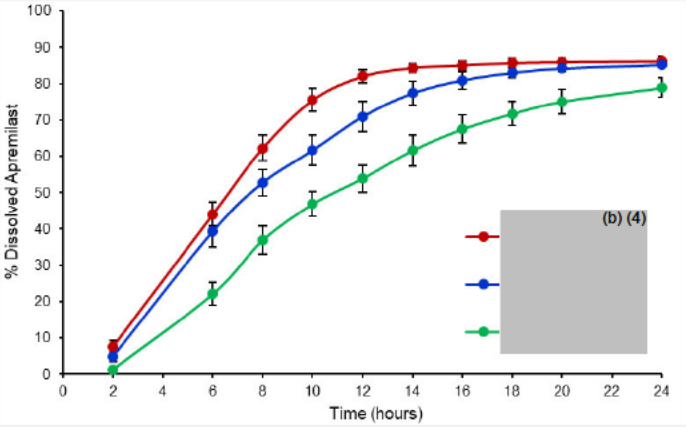
Figure 7. Dissolution profiles of Apremilast 75 mg (b) (4) Tablets with different (b) (4) (b) (4) amounts spiked in 0.5% Tween 80, pH 5.5, (b) (4) acetate buffer, 75 rpm, 37 °C, 900 mL



Effect of different ratio of (b) (4) on dissolution:

In the (b) (4) of the proposed Apremilast,75 mg (b) (4) tablet, (b) (4) (b) (4) (b) (4) The Applicant manufactured variant batches with different ratios of (b) (4) but with the same target (b) (4) As illustrated in Figure 8, drug release rate decreases with increasing (b) (4) ratio.

Figure 8. Dissolution profiles of Apremilast 75 mg (b) (4) Tablets with different (b) (4) in 0.5% Tween 80, pH 5.5, (b) (4) acetate buffer, 75 rpm, 37 °C, 900 mL

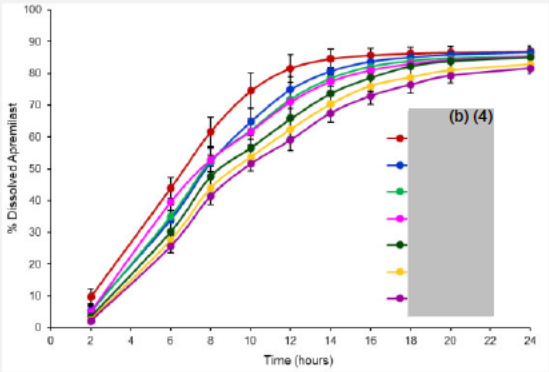


Effect of different (b) (4) on dissolution:

The apremilast 75 mg (b) (4) tablet cores are coated with a film coat of (b) (4) (b) (4) The Applicant manufactured variant batches with different (b) (4) with the same ratio of (b) (4) (b) (4) and compared their dissolution profiles with that of the target one ((b) (4) wt%).

As illustrated in Figure 9, drug release rate decreases as the (b) (4) increases. Significant change in dissolution profile is observed at (b) (4) % and (b) (4) % (b) (4)

Figure 9. Dissolution profiles of DP, Apremilast 75 mg (b) (4) Tablets with different (b) (4) in 0.5% Tween 80, pH 5.5, (b) (4) acetate buffer, 75 rpm, 37 °C, 900 mL



Reviewer's comment on the revised dissolution method:
The Applicant adequately justified the selection of the dissolution method parameters. The Applicant also shows that the method is able to discriminate changes in the amount of (b) (4) *. Based on the provided data/information in this submission, the proposed dissolution method is acceptable.*

3. Dissolution data and dissolution acceptance criteria

1) Dissolution data

The information of three exhibit batches is listed in Table 9. Batch 3203107R was used in Clinical Study 20200369 as Lot 1151718. Initially, the Applicant submitted the mean, range, and RSD of the dissolution data for the clinical and primary stability batches (3203107R, 3203108R, and 3203109R); however, they did not provide individual dissolution data for those batches. In Biopharmaceutics Information Request (IR) 1 (Appendix), this Reviewer requested the Applicant to submit the complete dissolution profile data (individual n=12 units/batch, mean, SD, RSD%, profile at all time points) of all batches. In response to IR 1, the Applicant provided the requested data, which are summarized in Table 10 by this Reviewer and shown in Figure 10.

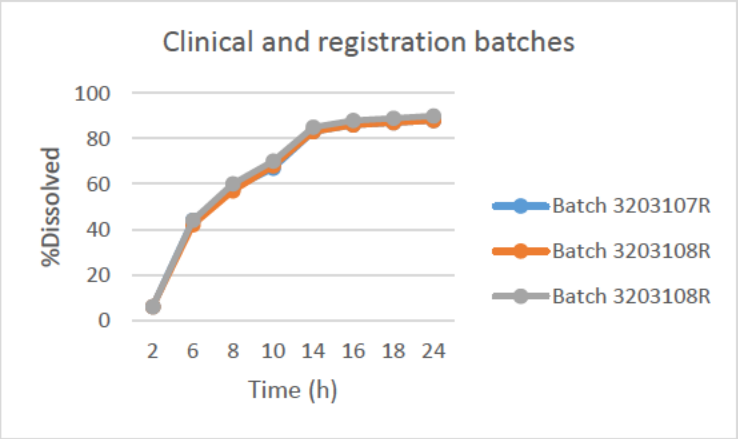
Table 9. List of all clinical and registration batches

Batch number	Batch size	Manufacturing date	Use of batch
3203107R	(b) (4) tablets	Jan 2022	Clinical Study 20200369 as lot 1151718, Primary stability
3203107R	tablets	Jan 2022	Primary stability
3203107R	tablets	Jan 2022	Primary stability

Table 10. Mean dissolution profile data of clinical and registration batches (n=12/batch)

Batch number/Time (h)	2	6	8	10	14	16	18	24
Batch 3203107R	6	44	58	67	83	86	87	88
Batch 3203108R	6	42	57	68	83	86	87	88
Batch 3203108R	6	44	60	70	85	88	89	90

Figure 10. Mean dissolution profile comparison of clinical and registration batches (n=12/batch)



It is important to note that the Applicant used (b) (4) However, a comparison of the dissolution profile data of new clinical and primary stability batches with those of the batches provided in the original submission shows significantly faster drug release from the new batches, especially at the later timepoints starting from 14 hours. In IR1, this Reviewer requested the Applicant to provide explanation and justification for the observed significant differences in test results (i.e., faster drug release of new batches). In IR 1 response, the Applicant explained that the dissolution method procedure was optimized (b) (4). Greater variability and occasional low outliers were observed using (b) (4), likely contributing to slower dissolution rates for batches provided in the original submission.

The Applicant also stated that (b) (4) impacts the dissolution rate of the drug product (DP), apremilast 75 mg (b) (4) tablet. The Applicant proactively implemented (b) (4)

2) Dissolution acceptance criteria

The Applicant proposed the following dissolution acceptance criteria:
2 h: NMT (b) (4)%
8 h: (b) (4)%
24 h: NLT (b) (4)%

Based on the dissolution data provided, the proposed dissolution acceptance criterion for the middle point (i.e., 8 h) is permissive and should be tightened. Biopharmaceutics IR 2 (Appendix) was sent to the Applicant for recommending the following acceptance criteria:

2 h: NMT (b) (4)%
8 h: (b) (4)%
24 h: NLT (b) (4)%

In the IR 2 response, the Applicant accepted the above recommended dissolution acceptance criteria.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: N/A

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: N/A

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: Adequate

The Applicant conducted an in vitro alcohol dose dumping study on proposed Apremilast 75 mg (b) (4) Tablets with 12 dosage units (n=12/batch) at multiple time-points up to 24 hours to obtain complete dissolution profiles in dissolution media 0.1N HCl and 0.5 % Tween 80 in sodium acetate buffer pH 5.5 containing 0, 5, 20, and 40 percent of alcohol (Tables 11-12; Figures 11-12).

Table 11. Mean dissolution data of Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with alcohol

Batch number/time(h)	1	2	6	8	10	12	14	16	18	24
Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with 0% alcohol	1	9	47	55	66	73	76	78	78	79
Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with 5% alcohol	1	7	45	55	67	75	79	81	82	82
Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with 10% alcohol	1	9	46	60	70	79	81	82	83	83
Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with 20% alcohol	1	6	39	54	60	73	78	83	85	87
Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with 40% alcohol	1	8	48	65	75	87	92	93	94	95

Table 12. Mean dissolution data of Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with alcohol

Batch number/time(h)	1	2	6	8	10	12	14	16	18	24
Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with 0% alcohol	0	4	33	42	49	52	54	56	56	58
Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with 5% alcohol	0	4	31	39	43	46	48	49	50	50
Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with 10% alcohol	0	3	29	37	42	45	47	48	49	51
Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with 20% alcohol	0	3	18	24	29	35	40	44	48	54
Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with 40% alcohol	1	6	28	40	50	63	74	82	86	89

Reviewer's assessment:

As shown in Table 11 and Figure 11, there is no alcohol-induced dose-dumping observed from the study conducted in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with alcohol, indicating that the presence of alcohol would have insignificant impact on drug release from the proposed ER drug product. Note that the mean % drug releases up to 2 hours are similar. The effect of 40% alcohol, 8-14% increases as seen in cumulative amount overtime, did not become apparent until after 10-12 hours. Results are deemed insignificant from a drug-release standpoint.

As shown in Table 13 and Figure 12, there is no alcohol-induced dose-dumping observed in 0.1 N HCl with alcohol up to 2 hours, indicating that the presence of alcohol would have

insignificant impact on drug release from the proposed ER drug product in the relevant physiologic condition with consumption of alcohol or alcohol beverages. The effect of 40% alcohol or noticeable separation in drug release profile, as seen in cumulative amount overtime, did not become apparent until after 10-12 hours encompassing the small intestine transit time, and reached approximately 31% higher vs. control. Note that all lower % alcohol concentrations (up to 20%) showed similar release profile, for which this Reviewer considered more clinically relevant. The clinical relevance of the results including the cumulative differences by 40% alcohol were conveyed to the Clinical review team.

It is noted that the Applicant did not propose pertinent labeling languages or instruction regarding clinical consequences with consumption of alcohol/alcoholic beverages with the proposed ER drug product, such as potential pharmacodynamic interaction and concerns for adequate disease control as a result of more rapid drug release as observed in in-vitro system. The above findings will be communicated to the Clinical and the Clinical Pharmacology review teams for proper labeling recommendations.

Figure 11. Mean dissolution profiles of Apremilast 75 mg (b) (4) Tablets in 0.5% Tween 80 in sodium acetate buffer pH 5.5 with alcohol

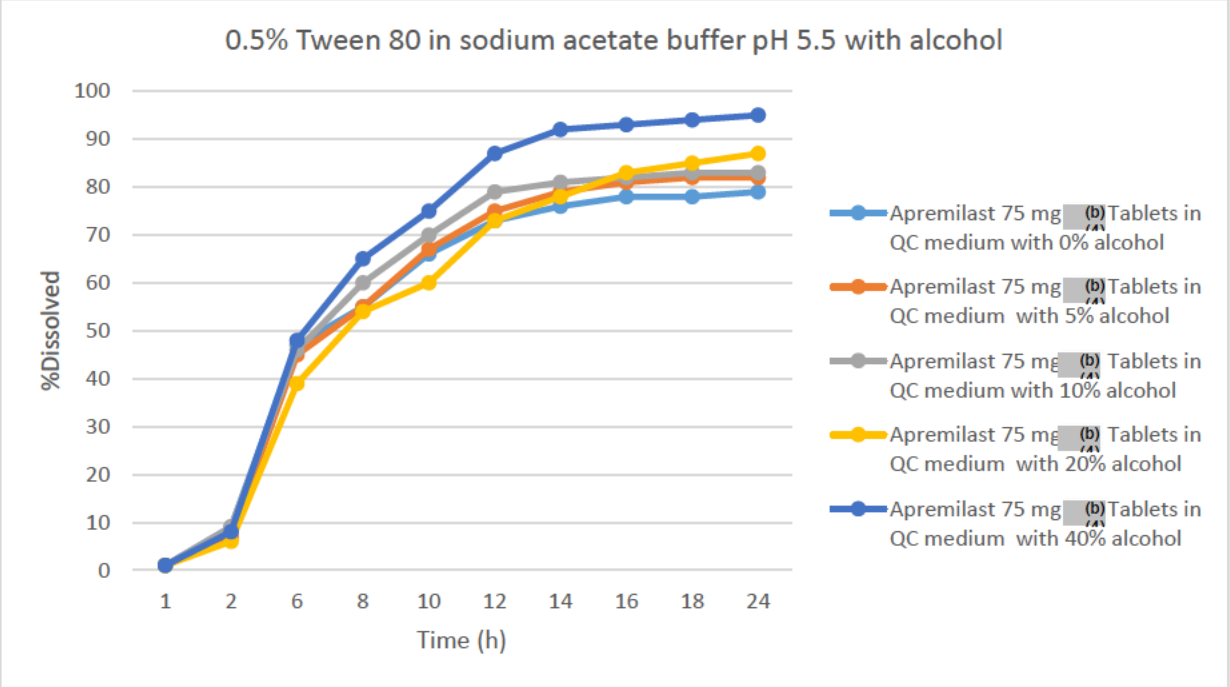
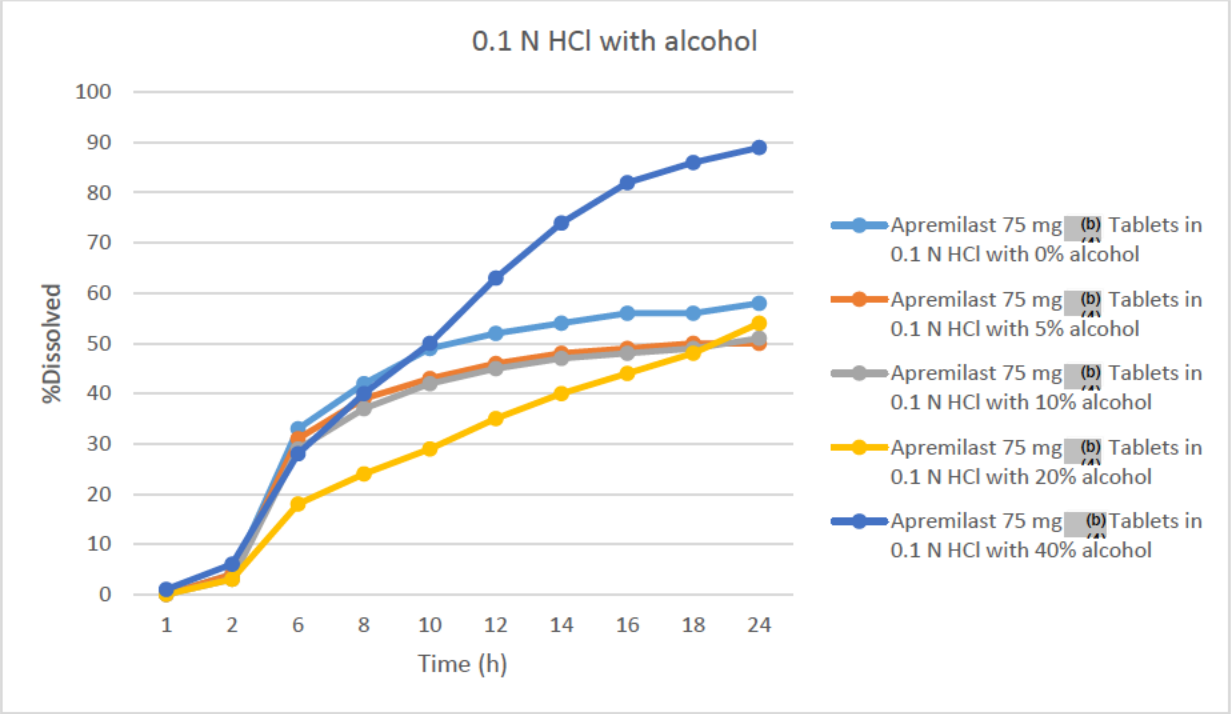


Figure 12. Mean dissolution profiles of Apremilast 75 mg (b) (4) Tablets in 0.1 N HCl with alcohol



B.11 EXTENDED-RELEASE DOSAGE FORMS –*Extended-Release Claim*

Assessment: ***{Adequate}***

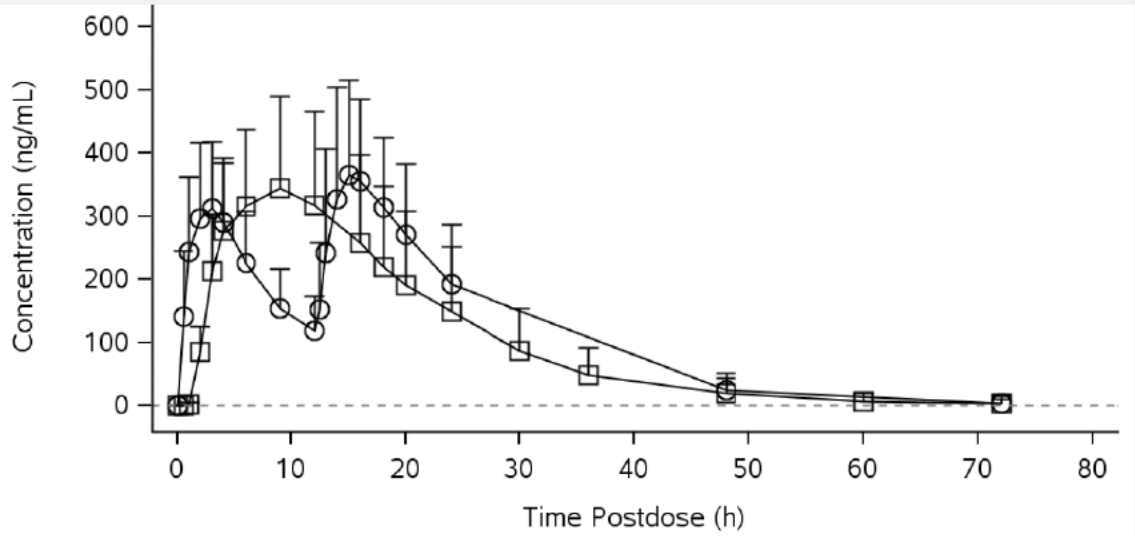
The provided information supports the "Extended-Release" claim for the proposed (b) (4) Extended-Release Tablets, (b) (4), per requirement described in the 21 CFR 320.25(f):

(i) The drug product meets the extended-release claims made for it.
(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose-dumping, assuring the quality of the ER drug product.
(iii) The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

1. ER characteristics of the proposed Apremilast 75 mg (b) (4) Tablets

Apremilast 75 mg (b) (4) Tablets is for once-daily (QD) dosing to reduce the frequency of administration and thereby improve patient compliance. In contrast, the LD- OTEZLA® immediate-release (IR) tablets (NDA 205437) is taken twice daily (BID). The clinical PK study (Study 20200369) showed that the mean Tmax (14.0 h) was prolonged for Apremilast 75 mg (b) (4) Tablets compared with that of the single dose LD (9.00 h).

Figure 13. Arithmetic mean (±SD) pharmacokinetic concentration-time profiles of Apremilast XR and IR formulations after a single dose on Day 1



As supportive evidence for drug release as designed, the extended-release characteristics of the proposed drug product were also demonstrated in in vitro test conditions (see B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA).

2. The bioavailability profile established for the drug product rules out the occurrence of any dose-dumping

No significant portion of the drug is quickly released in vivo, resulting in a potentially high concentration of the drug being introduced into the systemic circulation. The occurrence of dose dumping is ruled out.

3. The proposed drug product's steady-state performance is equivalent to a currently marketed immediate release drug product (i.e., OTEZLA® immediate-release (IR) tablets, NDA 205437)

The results of Study 20200369 show that the proposed Apremilast 75 mg (b) (4) Tablets (administered once daily) is bioequivalent to OTEZLA® immediate-release (IR) tablets 30 mg (NDA 205437, administered twice a day) at steady-state under fasted conditions in terms of Cmax and $AUC_{0\text{-}24h}$. Lower peak/trough fluctuation was observed after the QD dosing of the proposed ER tablets, compared to the LD (BID) (i.e., 3.01 vs 3.08).

Figure 14. Arithmetic mean (±SD) pharmacokinetic concentration-time profiles of Apremilast XR and IR formulations after repeated doses on Day 8

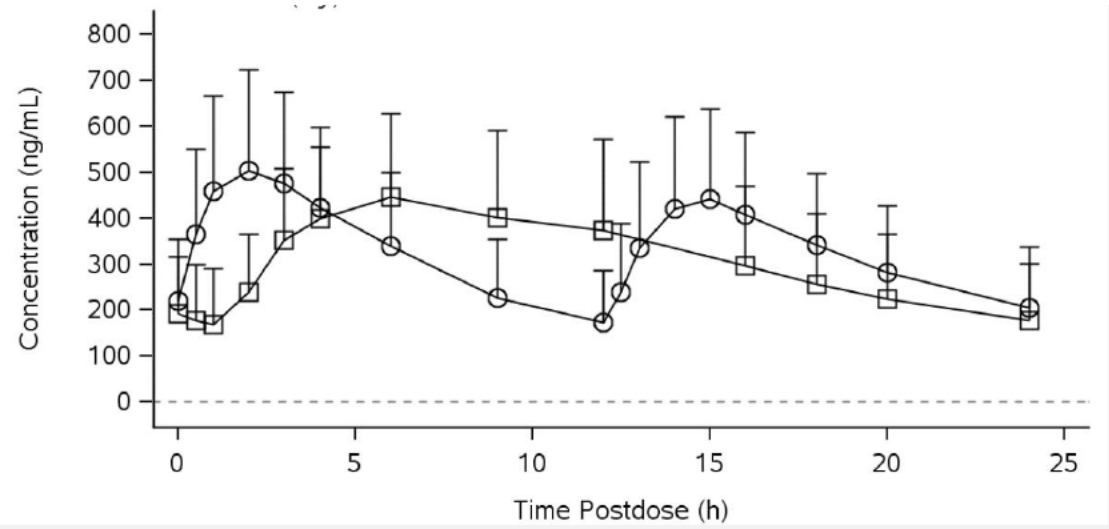


Table 13. Comparison of pharmacokinetic parameters between Apremilast XR and IR formulations on Day 8

Parameter	Treatment	n	GLSM	Test vs Reference	
				Ratio of GLSMs (90% CI)	Within-subject CV (%)
AUC_{0-24} (h*ng/mL)	Treatment B (reference)	189	7160		
	Treatment A (test)	196	6730	0.941 (0.896, 0.987)	29.0
C_{max} (ng/mL)	Treatment B (reference)	189	549		
	Treatment A (test)	196	467	0.851 (0.820, 0.883)	21.8

The PK results have been confirmed by the OCP reviewer.

4. The proposed drug product's formulation provides consistent pharmacokinetic performance between individual dosage units

The PK data of Study 20200369 show that the variability (mean %CV across the study) of Cmax, AUC0-t, and AUCinf is between 30.2% to 38.8% for the proposed drug product, as shown in Table 14.

Table 14. Summary of pharmacokinetic parameters (pharmacokinetic population) Day 1 (single-dose assessment)

Parameter	Treatment B (N = 203) GM (CV) [n]	Treatment A (N = 208) GM (CV) [n]
AUC_{last} (h•ng/mL)	8150 (38.8) [187]	6520 (60.9) [200]
AUC_{inf} (h•ng/mL)	8270 (38.2) [185]	6620 (59.4) [199]
C_{max} (ng/mL)	440 (30.2) [187]	380 (36.3) [200]
t_{max} (h)	14.0 (0.500-24.0) [187]	9.00 (3.00-18.0) [200]
t_{lag} (h)	0 (0-0) [187]	0.500 (0-1.05) [200]
$t_{1/2}$ (h)	7.68 (2.19) [185]	7.77 (2.43) [199]
λ_z (1/h)	0.0935 (27.0) [185]	0.0930 (29.5) [199]
CL/F (L/h)	7.25 (38.2) [185]	11.3 (59.4) [199]
V_z/F (L)	77.5 (32.5) [185]	122 (56.3) [199]

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

The commercial formulation is the same as the one used in pivotal relative BA/BE study.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date:
Hansong Chen, PharmD, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Ta-Chen Wu, Ph.D.

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

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 7/21/2025 05:54:12PM
GUID: 508da6df000269e151ff37cd8f4e13a1

Hansong Chen

Digitally signed by Hansong Chen
Date: 7/21/2025 03:12:09PM
GUID: 525d7d660003845a197a2e1682433d0d

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	210745
Assessment Cycle Number	1
Drug Product Name	Otezla XR (apremilast) extended-release tablets, 75 mg

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN 0017
28-Day Treatment Initiation Pack 41-count -**Wallet**	Adequate	SDN 0025
28-Day Treatment Initiation Pack 41-count -**Sleeve**	Adequate	SDN 0025
30-count **Bottle**	Adequate	SDN 0017

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0017	Oct 30, 2024	Labeling, PI, C/C labels
0025	Apr 04, 2025	C/C labels

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Submitted on Oct 30, 2024 SDN 0017

(b) (4)

Item	Items 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		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	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 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.	N/A	
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).	N/A	

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

1.1 FULL PRESCRIBING INFORMATION

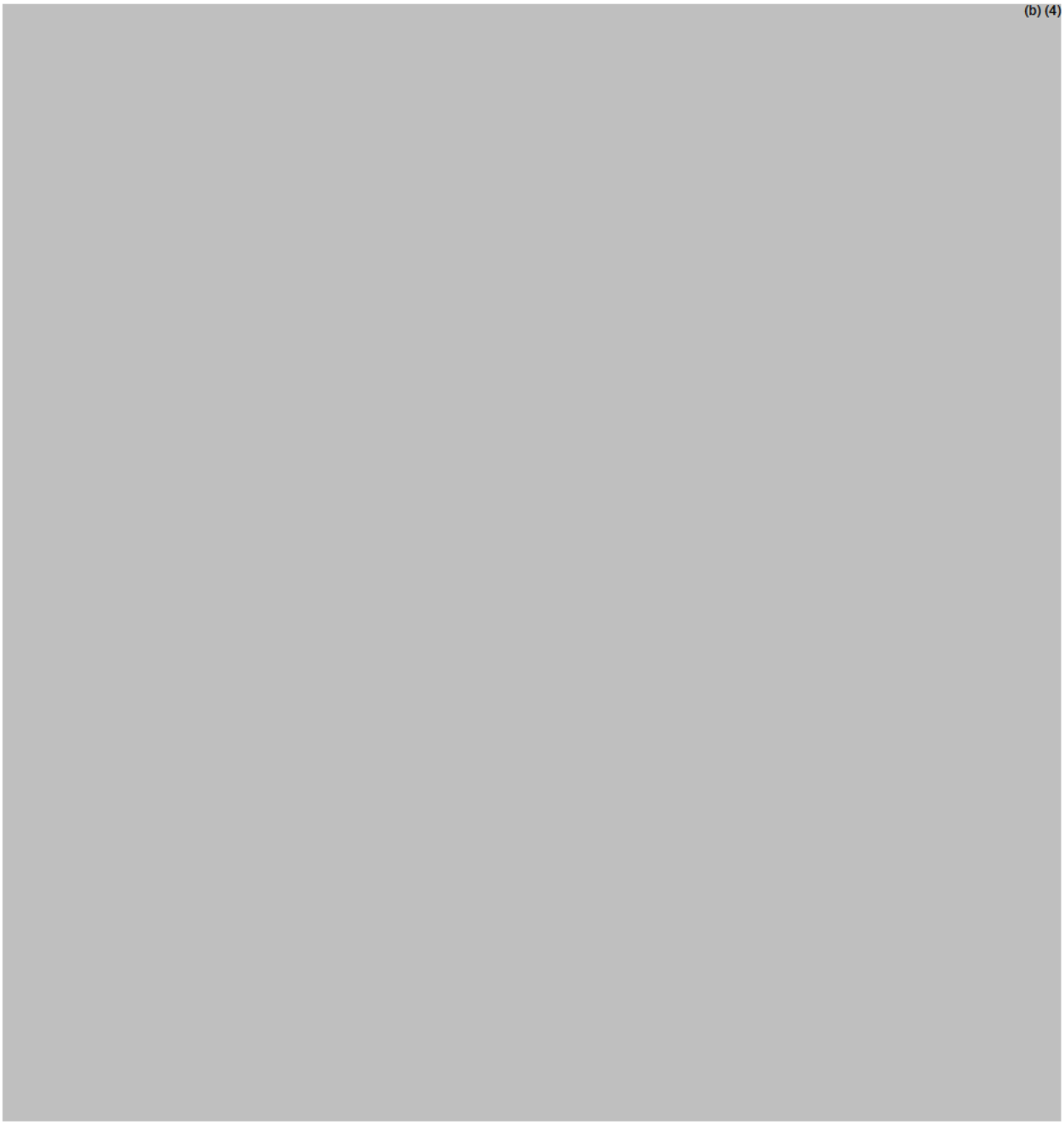
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Items 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	
Strength(s) in metric system	Adequate	
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 (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	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 parental 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.	N/A	

1.2.2 Section 3 (Section 11 DESCRIPTION)

(b) (4)



Item	Items 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)	**Inadequate**	**Include the established name, apremilast, in the drug product names and revise the drug product names as shown below.** • OTEZLA (apremilast) tablets • OTEZLA XR (apremilast) extended-release tablets
Dosage form(s) and route(s) of administration	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)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	**Inadequate**	**List inactive ingredients 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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	**Inadequate**	**Add physical properties of the drug substance, apremilast, as shown in red above.**

Section 11 (DESCRIPTION) Continued

Item	Items 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 oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

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

Item	Items 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		
Available dosage form(s)	**Inadequate**	**Separate each tablet description as shown above in red.**
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	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 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.	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 numerical citation to "OSHA Hazardous Drugs."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	**Inadequate**	• **Delete the storage conditions statements below** (b) (4) • **Add the following storage conditions statement.** Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]

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."*	N/A	
Include information about child-resistant packaging (if manufacturer choose to include)	Adequate	

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

Item	Items 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)
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	

CONTAINER AND CARTON LABELING: Submitted on Apr 04, 2024 SDN 0025

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Wallet Label (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	**Inadequate**	• **Delete the storage conditions statements below** (b) (4) [redacted] • **Add the following storage conditions statement.** Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	

If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap Overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others if space is available.	N/A	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about **Sleeve Label** (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	**Inadequate**	**Add "Lot:" and "Exp:".**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	**Inadequate**	• **Delete the storage conditions statements below** (b) (4) • **Add the following storage conditions statement.** Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap Overseal, unless a cautionary statement is required.	N/A	

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others if space is available.	N/A	

Bottle 30-Count

(b) (4)

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about **Bottle Label** (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	**Inadequate**	**Add "Lot:" and "Exp:".**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	**Inadequate**	• **Delete the storage conditions statements below** (b) (4) [redacted] • **Add the following storage conditions statement.** Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap Overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others if space is available.	N/A	

Assessment of PI: *ADEQUATE*

Assessment of Carton and Container Labeling: *ADEQUATE*

Assessment of Medication Guide: *ADEQUATE*

ITEMS FOR ADDITIONAL ASSESSMENT: *None*

Overall Assessment and Recommendation:

The PI and the container/caron labels are satisfactory from the CMC perspective.

This NDA is recommended for "Approval" from the CMC labeling perspective.

As shown in red above the edits in the PI are made and conveyed to the applicant.

The following comments regarding ONLY the wallet, sleeve and bottle labels should be conveyed to the NDA applicant:

- **Delete the storage conditions statement.**
- **Add the following storage conditions statement.**
  Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature
- **Add "Lot:" and "Exp:" to sleeve and bottle labels.**

Primary Labeling Assessor Name and Date:
Hitesh Shroff
CDER/OPQ/OPQAII/DPQAVII
May 28, 2025

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

Julia Pinto, Ph.D.
Supervisory Chemist
CDER/OPQ/OPQAII/DPQAVIII

Hitesh Shroff

Digitally signed by Hitesh Shroff
Date: 5/28/2025 03:13:44PM
GUID: 502d1ab500002afd219fd67e3b9c99c8

Julia Pinto

Digitally signed by Julia Pinto
Date: 5/28/2025 03:17:39PM
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/

CRAIG M BERTHA
07/22/2025 07:55:09 AM