

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211723Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 211-723 Assessment #1

Drug Product Name	Tazverik (tazemetostat) tablets
Dosage Form	Tablets
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Epizyme
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001 Original Submission	23-May-2019	All OPQ
0002 Label amendment	30-May-2019	DP
0005 Label Amendment	12-Jul-2019	DP
0010 Label Amendment	9-Aug-2019	DP
0014 CMC Amendment	22-Aug-2019	DP
0017 CMC Amendment	5-Sep-2019	Biopharm
0018 CMC Amendment	5-Sep-2019	Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Daniel Jansen	Suong Tran
Drug Product	Tefsit Bekele	Anamitro Banerjee
Manufacturing	Quamrul Majumder	Rakhi Shah
Microbiology	Quamrul Majumder	Rakhi Shah
Biopharmaceutics	Kaushalkumar Dave	Banu Zolnik
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Olen Stephens	
Laboratory (OTR)	NA	NA
Environmental	Raanan Bloom	NA

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 211-723 is recommended for approval from OPQ. All manufacturing and labeling sites are adequate and there are no pending review issues nor any recommended PMR/PMC actions from OPQ. A shelf life of 24 months is granted when the tablets are stored below 30°C (86°F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Epizyme, Inc. submitted NDA 211-723 for Tazverik (tazemetostat) tablets, 200 mg, indicated for the treatment of adult patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery. FDA granted Fast Track and Orphan Designation for this indication. Epizyme has requested accelerated approval. Tazemetostat is a new molecular entity that has low solubility, but high permeability. The drug product is supplied as red, round, biconvex, film-coated 200 mg tablets, debossed on one side with the dosage strength and the letters EZM. The proposed dose is 800 mg twice daily. The tablets are packaged in bottles of 240 tablets with a desiccant (a one-month supply). The recommended storage is below 30°C (86°F) and the applicant is requesting a 24-month shelf life. Tablets are to be administered whole with or without food. No provisions in the package insert allow for extemporaneous solutions that enable dosing to pediatric patients or patients who have trouble swallowing.

The drug product is

(b) (4)

The manufacturing process has remained consistent through development and into the proposed commercial process, changing only sites and batch size. Bridging to early formulations and dosage strengths was not necessary.

Drug substance and drug product specified impurities are limited based on qualification studies. The nonclinical reviewer verified these proposed limits are qualified and acceptable.

No biowaiver request was submitted or required for the proposed Tazemetostat Tablets, 200 mg. The Applicant performed clinical (safety and efficacy) studies (Studies E7438-G000-101, EZH-202, EZH-203 and EZH-501 for safety, and Study #EZH-202 for efficacy) to support the 505(b)(1) submission with the intended commercial formulation.

The primary issue cutting across the review disciplines was that the applicant proposed a single tier control for the particle size distribution, controlling the d_{90} of the drug substance at (b) (4) μm . Particle size for the drug substance is typically controlled with three tiers of acceptance criteria at d_{10} , d_{50} , and d_{90} . The risks to inappropriate drug substance particle size control are manufacturability challenges (b) (4), impacts on in vitro release, content uniformity of dosage units and assay. The drug product formulation has a (b) (4)% drug load, which the OPQ process reviewer confirmed helps to mitigate manufacturability issues. No impact has been seen for batches manufactured with drug substance in this particle size distribution. Similarly, the content uniformity and assay data suggests (b) (4) with this size distribution. The OPQ biopharmaceutics reviewer confirmed that the sponsor evaluated three lots with d_{90} values of (b) (4) μm , (b) (4) μm , and (b) (4) μm . These batches are different from each in terms of their dissolution, with f_2 value being lower than 50. However, all three batches show nearly complete dissolution by 30 minutes, and the proposed product has T_{max} of in the range of 1-2 hour. Therefore, the difference in dissolution trend during first 30 minutes may not have clinical implications. Finally, the drug substance manufacturing process (b) (4) consistently generates drug substance batches with d_{90} values in the (b) (4) μm range. The applicant's proposed particle size distribution controls were accepted.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of adult patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery
Duration of Treatment	Treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	1,600 mg/day (800 mg BID)
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance is the mono-hydrobromide salt of tazemetostat, a small synthetic molecule. It has been well characterized using state-of-the-art methods regarding its physicochemical characteristics and structure. Polymorph (b) (4) that results from the described synthesis, and the drug substance specification includes polymorph testing. The information provided in the application demonstrated consistent production of tazemetostat achieving a well-defined quality for the tazemetostat drug substance. The synthesis, down-stream processes and purification of the active substance are

adequately controlled. Starting materials are designated as per ICH Q11. Controls of residual solvents, elemental impurities, and mutagenic impurities comply with applicable ICH guidances. Limits above (b) (4)% on specified impurities are found adequate by the Pharmacology Toxicology team. Methods to control the quality of the drug substance are adequate.

Stability data support an expiry of (b) (4) months for the tazemetostat drug substance when stored in (b) (4)

There are no approvability issues for the drug substance portion of this application. There are no deficiencies that need to be reported to the applicant with respect to the drug substance portion of this application. The data is adequate to support the use of tazemetostat drug substance in the manufacture of tazemetostat drug product.

Drug Product: Adequate

Tazemetostat is a new molecular entity that has not been previously studied or approved and the applicant submitted this NDA for tazemetostat under the 505(b)(1) pathway. The drug product is supplied as red, round, biconvex, film coated 200 mg tablets. The tablets are debossed on one side with "200 EZM". 240 tablet counts are packaged in HDPE bottles with desiccant and stored at < 30 °C. The applicant provided satisfactory drug product information including adequate stability data for TAZVERIK (tazemetostat). Tazemetostat is a selective, S-adenosylmethionine-competitive inhibitor of enhancer of zeste homolog 2, a histone methyltransferase. It is indicated for the treatment of adult patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery. The drug product is formulated as immediate release tablet containing tazemetostat hydrobromide and common pharmaceutical excipients: lactose monohydrate, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate. The tablets are film-coated with (b) (4) (b) (4) red. The drug substance, tazemetostat hydrobromide is a crystalline material (b) (4)

The 12-months stability studies at long-term (25°C/60%RH) and intermediate (30°C/75%RH) storage conditions support the proposed storage conditions of "do not store above 30°C". Based on the 12 months available data at long term and 6 months at accelerated storage conditions, 24 months expiration date may be granted.

Labeling: Adequate

Minor labeling changes were suggested to the clinical division and communicated through the clinical PM. At the time of this executive

summary, labeling negotiation is on-going and there are no major CMC related concerns.

Manufacturing: Adequate

Refer to the executive summary regarding the impact of the formulation on manufacturing process controls. Management controls are not in place if equipment types or make are changed, but the applicant had demonstrated enough (b) (4) understanding for such change, if needed, without affecting DP CQA. The batch formula (b) (4) does not reveal any manufacturing risks beyond the typical risks for IR dosage form.

The manufacturing process was initially developed by (b) (4) up to a scale of (b) (4). At that stage, Epizyme assumed responsibility for the project and continued development activities at (b) (4) where the process was scaled-up to (b) (4). Patheon (Cincinnati, OH, part of Thermo Fisher Scientific) was selected as the commercial manufacturing site. At Patheon the process was scaled-up to the proposed commercial batch size of (b) (4).

The firm, Patheon Pharmaceuticals Inc. EFI# 1510437 an CMO for DP manufacturing. It has acceptable "TCM" profile and approval based on CGMP.

The firm, Sterling Pharma Solutions Limited EFI#3002806719 listed as DS manufacturer, has acceptable "CSN" profile and approval based on CGMP.

Biopharmaceutics: Adequate

The Applicant first investigated the solubility of tazemetostat HBr in various aqueous media and reported the highest solubility in the pH range of 1-4. As 0.1N HCl represents the in vivo pH condition of the stomach, it is the most commonly used and preferred dissolution medium for IR products. The Applicant's selection of 0.1N HCl as the dissolution medium is appropriate as the proposed product is an IR formulation and the Applicant reported that this medium provides sink condition, stability against drug degradation and complete dissolution of the proposed product with low variability. For selection of the volume and apparatus for dissolution testing, the Applicant performed dissolution of the test product in (b) (4) and 900 mL 0.1N HCl using USP Apparatus 2, and (b) (4). The provided data show no difference in the dissolution profile/behavior among the studied groups. Therefore, the applicant selected USP Apparatus 2 with 900 mL for testing discriminating ability of the method. In general, when no difference in dissolution is observed (b) (4) of dissolution medium and if both the media can provide sink conditions (which is the case for the proposed

product) (b) (4) should be selected for the dissolution method. While the Applicant could have selected (b) (4) as the dissolution medium volume, the Applicant's selection of 900 mL as the dissolution medium volume is acceptable because the Applicant has adequately demonstrated the discriminating ability of the proposed method towards the critical attributes/variables.

The Applicant's proposed dissolution acceptance criterion of 'NLT (b) (4) % (Q) at 30 minutes' is based on the dissolution data from the clinical batches. Also, the data from the discriminating ability studies indicate that the proposed dissolution method with dissolution acceptance criterion of 'NLT (b) (4) % (Q) at 30 minutes' is likely to identify deviation in the product's quality. Based on the provided information/data, the proposed dissolution acceptance criterion is deemed 'adequate' for quality control testing of the proposed product.

Microbiology (if applicable): Adequate

The drug product is a solid oral dosage form. (b) (4)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay at Release and Stability	Strong drug substance stability	Low	(b) (4)	Acceptable	
Physical Stability (solid state)	(b) (4)	Medium		Acceptable	
Content Uniformity	Single tier, d ₉₀ PSD for DS	Low		Acceptable	
Microbial Limits	(b) (4)	Low		Acceptable	

Dissolution	Low solubility drug substance; single tier DS PSD control	Medium	(b) (4)	Acceptable	
-------------	---	--------	---------	------------	--

D. List of Deficiencies for Complete Response

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

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

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

None

Application Technical Lead Name and Date: Olen Stephens 10/16/19

55 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Reviewer's assessment of applicant's response.

The response is acceptable as the new post approval stability protocol reflects the proposed storage conditions of (b) (4)

R Regional Information

Environmental Analysis

Tazemetostat is a new molecular entity and the environmental analysis team was consulted regarding its impact on the environment. James Laurensen provided the following statement:

Information provided by the applicant and QSAR modelling for estrogen receptor (ER) and androgen receptor (AR) activity, indicates a low potential for tazemetostat interaction with estrogen and androgen receptors. Animal (rat, rabbit) studies indicate that tazemetostat exhibits a potential for teratogenicity at mg/kg levels. The Fish Plasma Model output indicates that additional chronic studies may be required. Modeled aquatic toxicity results show a large margin between exposure concentrations and effects. Based on the expected low exposure concentrations of tazemetostat (EIC = (b) (4) µg/L; EEC = (b) (4) µg/L) and low water solubility, significant environmental impacts are not expected due to approval of this application. Future applications that significantly increase tazemetostat usage may require additional studies on the potential for developmental effects in aquatic organisms.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.

Reviewer's Assessment: Adequate.

The applicant's request for categorical exclusion is granted.

Primary Drug Product Reviewer Name and Date: Tefsit Bekele October 03, 2019

Secondary Reviewer Name and Date: Anamitro Banerjee October 11, 2019

CHAPTER III: ENVIRONMENTAL
[IQA NDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

Environmental Analysis

Application: NDA 211723

Drug product: Tazemetostat Tablets for oral use

Indication: EZH2 inhibitor indicated for the treatment of patients with metastatic or locally advanced epithelioid sarcoma not eligible for curative surgery

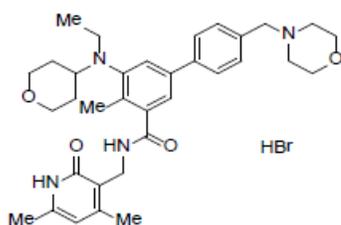
Proposed doses: Recommended dose is 800 mg taken orally twice daily

Reviewer's Assessment: Adequate

Information provided by the applicant and QSAR modelling for estrogen receptor (ER) and androgen receptor (AR) activity, indicates a low potential for tazemetostat interaction with estrogen and androgen receptors. Animal (rat, rabbit) studies indicate that tazemetostat exhibits a potential for teratogenicity at mg/kg levels. The Fish Plasma Model output indicates that additional chronic studies may be required. Modeled aquatic toxicity results show a large margin between exposure concentrations and effects. Based on the expected low exposure concentrations of tazemetostat (EIC = (b) (4) µg/L; EEC = (b) (4) µg/L) and low water solubility, significant environmental impacts are not expected due to approval of this application. Future applications that significantly increase tazemetostat usage may require additional studies on the potential for developmental effects in aquatic organisms.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.

Structural Formula:



MW: 572.75 g/mol (free base)

Mechanism of action: Tazemetostat is a selective, orally bioavailable, small molecule inhibitor of the enhancer of zeste homolog 2 (EZH2), a histone methyltransferase. EZH2 is the catalytic subunit of the polycomb repressive complex 2, catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3, which leads to repression (transcriptional regulation) of certain important gene sets such as tumor suppressors, differentiation markers, cell cycle regulators, and apoptotic machinery.

Claim of Categorical Exclusion: The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of no extraordinary circumstances under 21 CFR 25.21. Supporting information is provided in a 6/12/2018 Environmental Risk Assessment (prepared by (b) (4)), which provides environmental concentration information and potential biota effects. Information on effects on biota is not provided. An estimated environmental concentration is provided (see below). No environmental effects studies were prepared by the applicant.

Environmental Exposure: Using a production estimate of (b) (4) tazemetostat/yr as a worst-case estimate, (the maximum active ingredient production for sale within 5 years of initial marketing) the total amount of tazemetostat introduced into the aquatic environment at discharge from WWTPs (EIC: expected introductory concentration) as a result of the use of this product is estimated at (b) (4) µg/L. The estimated environmental concentration or EEC is (b) (4) µg/L.

Tazemetostat hydrobromide was considered very slightly soluble at pH 5, and practically-insoluble/ insoluble at pH 6.5 and 7.4

Application Review: In evaluation of the claim for categorical exclusion, in addition to the provided information, the following models were used:

I. Model Predictions

1. Fish Plasma Model

- The fish plasma model is used for comparative hazard identification.
- Calculated using human therapeutic concentration and Cmax associated with NOAEL from toxicity studies.
- Cmax (human therapeutic concentration) = 933 ng/mL (after multiple-dose administration of 800 mg tazemetostat; from label).
- Production volume = (b) (4)/year. Expected Introduction Concentration (EIC) = (b) (4) µg/L (no dilution); expected environmental concentration (EEC) = (b) (4) µg/L (10x dilution)
- Log P = (b) (4) Log D pH= (b) (4)
- Fish plasma model result (ER (b) (4)) indicate fish chronic studies may be needed.

2. Aquatic Toxicity predictions (Danish QSAR DB)

Aquatic toxicity predictions for tazemetostat are not reported in the Danish QSAR toolbox database. Data for top 4 analogues were retrieved. Three analogues have similarity index of (b) (4) and one analogue has similarity index of (b) (4).

Fathead minnow: 96h LC50 estimated to range from (b) (4) to (b) (4) mg/L = (b) (4) µg/L
Daphnia magna: 48h EC50 estimated to range from (b) (4) to (b) (4) mg/L = (b) (4) µg/L
Pseudokirchneriella s.: 72h EC50 estimated to range from (b) (4) to (b) (4) mg/L = (b) (4) µg/L

The lowest predicted acute toxicity value ((b) (4) µg/L) is (b) (4) than the EIC ((b) (4) µg/L); (b) (4) than the EEC.

3. ECOSAR

QSAR predictions for acute and chronic effects

Functional groups predicted: aliphatic amines, acrylamides, amides

3.1 Acute Toxicity

Lowest predicted acute toxicity value for fish (LC50_96h): (b) (4) mg/L = (b) (4) µg/L

Lowest predicted acute toxicity value for Daphnid (LC50_48h): (b) (4) mg/L = (b) (4) µg/L

Lowest predicted acute toxicity values for green algae (EC50_96h): (b) (4) mg/L = (b) (4) µg/L

Predicted acute toxicity value for most sensitive organism (algae) is (b) (4) than the EIC.

3.2 Chronic Toxicity

Lowest predicted chronic toxicity value for fish: (b) (4) mg/L = (b) (4) µg/L

Lowest predicted chronic toxicity value for Daphnid: (b) (4) mg/L = (b) (4) µg/L

Lowest predicted chronic toxicity value for green algae: (b) (4) mg/L = (b) (4) µg/L

Lowest predicted chronic toxicity value for most sensitive organisms (fish and Daphnid) is (b) (4) than the EIC; (b) (4) than the EEC.

4. T.E.S.T Model predictions (EPA's COMPTOX application)

<https://comptox.epa.gov/dashboard/predictions/index>

4.1 Acute Toxicity predictions

Lowest predicted acute toxicity values for fathead minnow (LC50_96h): (b) (4) mg/L = (b) (4) µg/L

Lowest predicted acute toxicity values for Daphnid (LC50_48h): (b) (4) mg/L = (b) (4) µg/L

Lowest predicted acute toxicity values for protozoa (IGC50_48h): (b) (4) mg/L = (b) (4) µg/L

Predicted acute toxicity value for most sensitive organism (fish) is (b) (4) than the EIC ((b) (4) µg/L), (b) (4) than the EEC.

5. QSARs for estrogen receptor (ER) and androgen receptor (AR) activity:

Predictions for ER activity NOT reported in Mansouri et al., 2016 (CERAPP)

ER models (OCHEM/CERAPP): INACTIVE in ER binding and agonist models ((b) (4) % accuracy); ACTIVE (very weak) in ER antagonist model ((b) (4) % accuracy)

AR models (OCHEM/COMPARA): ACTIVE (very weak) in AR binding, and antagonist models ((b) (4) % accuracy); INACTIVE in agonist model ((b) (4) % accuracy)

II. Animal Studies

The no-observed-adverse-effect level (NOAEL) for maternal effects in rats was 100 mg/kg/day. The NOAEL for maternal effects in rabbits was 400 mg/kg/day. A developmental NOAEL for rats or rabbits was not determined. In repeat-dose toxicity studies in rats or monkeys treated orally with up to 600 mg/kg/day for 13 weeks, no adverse effects on reproductive organs were observed.

Primary Environmental Assessor Name and Date: Raanan Bloom

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

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME (Tazverik)	Adequate
Established name(s)	Tazemetostat	Adequate
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	200 mg	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	

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)	N/A	

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)	Tablets	Adequate
Strength(s) in metric system	200 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Follows salt policy	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	TRADENAME (tazemetostat) is an immediate release film coated tablet containing 200 mg tazemetostat	Tablets: 200 mg, film-coated, red, round biconvex shape and debossed with "EZM 200" on one side and plain on the other.
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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME and tazemetostat	Adequate
Dosage form(s) and route(s) of administration	Tablets for oral use	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	TRADENAME (tazemetostat) tablets for oral use contain 200 mg tazemetostat equivalent to 228 mg tazemetostat hydrobromide.	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	<p>Each TRADENAME tablet contains the following inactive ingredients</p> <ul style="list-style-type: none"> • Tablet: lactose monohydrate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. • Film-coat: hypromellose, talc, polyethylene glycol, 	Adequate. Changed the format to: Each TRADENAME tablet is film-coated and contains the following inactive ingredients in the tablet core: lactose monohydrate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, sodium starch glycolate, and magnesium stearate. The film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and red iron oxide.

	titanium dioxide, iron oxide (red).	
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	
Statement of being sterile (if applicable)	N/A	
Pharmacological/therapeutic class	(b) (4) methyltransferase inhibitor	Adequate
Chemical name, structural formula, molecular weight	<p>Chemical name: [1,1'-Biphenyl]-3-carboxamide, <i>N</i>-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2<i>H</i>-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-, hydrobromide (1:1).</p> <p>Structural formula: provided</p> <p>Molecular weight: 653.66 g/mol</p>	Adequate

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	None	pH and pKa information was requested to be included

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablet	
Strength(s) in metric system	200 mg	
Available units (e.g., bottles of 100 tablets)	Bottles of 240 tablets with a desiccant	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	TRADENAME 200 mg film-coated tablets are red, round biconvex shape and debossed with "EZM 200" on one side and plain on the other. NDC 72607-100-00	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	

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.)	N/A	Adequate
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."	Not included in this section however, in section 3.2.P.7 <i>container closure system</i> it is indicated that the canisters (b) (4)	Adequate. The size and shape of the canister is different from the product
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Do not store above 30°C (86°F).	(b) (4) statement has been added
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	N/A	Not relevant for oral dosage forms

latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	(b) (4)	This is not required but the applicant can choose to include this information. (b) (4)

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	Manufactured for: Epizyme, Inc. 400 Technology Square Cambridge, MA 02139	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Provided	Adequate
Dosage strength	Provided	Adequate
Route of administration	Provided	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Provided	Adequate, however CMC recommends the statement to be moved to the side of the panel due to overcrowding of the space around the name and strength
Net contents (e.g. tablet count)	Provided	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Space provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage conditions provided	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Bar code	Provided	Adequate
----------	----------	----------

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	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	-	

Assessment of Carton and Container Labeling: Adequate

Overall Assessment and Recommendation:

The container label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of what are noted in the Assessor's Comments column above.

Primary Labeling Assessor Name and Date: Tefsit Bekele 9/19/2019

Secondary Assessor Name and Date Anamitro Banerjee 10/11/2019

Issues identified and PAI resolution	
A two item FDA form 483 is issued. The firm seems does not have good laboratory practice.	
Request for Additional Information (#RAI) and Response	
Inspection outcome	Approve . Decision is made based on CSO and DFR recommendation without EIR and Firm's 483 response.

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table
None

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Quamrul Majumder	Rakhi Shah	6/19/2019	Choose an item. TBD	TBD
2	Quamrul Majumder	Rakhi Shah	7/23/2019	IR	TBD
3	Quamrul Majumder	Rakhi Shah	8/21/2019	IR	TBD
4	Quamrul Majumder	Rakhi Shah	9/9/2019	Adequate	Approve

BIOPHARMACEUTICS

<p>Application No: NDA 211723; 505(b)(1)</p> <p>Drug Product Name/Strengths: Tazemetostat Tablets/200 mg</p> <p>Route of Administration: Oral</p> <p>Indication: Treatment of adult patients with metastatic or locally advanced epithelioid sarcoma</p> <p>Applicant Name: Epizyme, Inc.</p> <p>Date of Submission: 05/23/2019 (Original)</p> <p>Primary Reviewer: Kaushalkumar Dave, Ph.D.</p>
--

Secondary Reviewer: Banu Zolnik, Ph.D.

REVIEW SUMMARY

Submission: The proposed drug product, Tazemetostat Tablets; 200 mg, is an immediate-release (IR) product for oral administration. This NDA is a 505(b)(1) submission where the Applicant has substantially investigated the safety and efficacy of Tazemetostat by performing multiple clinical studies. The proposed product is indicated for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery. The proposed dosage is 800 mg BID orally, until disease progression or intolerability for patients.

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 conducted various studies and provided justifications for selection of the suitable dissolution testing conditions. The proposed dissolution method for the proposed Tazemetostat Tablets; 200 mg, is as follows: *900 mL of 0.1N HCl using USP Apparatus 2 (paddle) at 50 rpm*. The Applicant prepared several test batches to investigate the discriminating ability of the proposed product. The provided dissolution data show that the proposed dissolution method can discriminate between the target product and the deviant batch prepared with change in composition (b) (4) drug substance particle size distribution, drug substance polymorphs, (b) (4) (b) (4) and tablet hardness. The applicant's selection of the critical attributes/variables and their levels are reasonable and therefore acceptable. The Applicant has adequately demonstrated the discriminating ability of the proposed dissolution method. Based on the Applicant's appropriate selection of the dissolution testing conditions, and the provided data demonstrating discriminating ability, the proposed dissolution method is deemed adequate for quality control testing of the proposed product.

Dissolution Acceptance Criterion: The Applicant's proposed dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 30 minutes' is based on the dissolution data from the clinical batches. Also, the data from the discriminating ability studies indicate that the proposed dissolution method with dissolution acceptance criterion of 'NLT (b) (4)% (Q) at 30 minutes' is likely to identify deviation in the product's quality. Based on the provided information/data, the proposed dissolution acceptance criterion is deemed 'adequate' for quality control testing of the proposed product.

The final and approved dissolution method and 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	900 mL
Medium	0.1N HCl
Temperature	37.0 ± 0.5 C
Acceptance Criterion	NLT ^(b) ₍₄₎ % (Q) at 30 minutes

Formulation Bridging: In-vitro or in-vivo bridging study is not needed for the proposed product, as there were no changes made in (i) composition for the clinical batches, exhibit batches, and proposed commercial drug product, (ii) product manufacturing site, and (iii) manufacturing process in the scale-up.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 211723 for Tazemetostat Tablets; 200 mg, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	Received date	Document
0001	05/23/2019	Original NDA Submission
0017	09/05/2019	Quality/Response to Information Request

BACKGROUND

Tazemetostat is an inhibitor of the histone methyltransferase (HMT) enhancer of zeste homolog 2 (EZH2). Tazemetostat is indicated for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery. The proposed product is developed a single-strength (200 mg) immediate-release tablets for oral administration and submitted under 505(b)(1) pathway. The proposed dosage is 800 mg BID orally, until disease progression or intolerability for patients.

The Applicant explored 100 mg, 200 mg and 400 mg strengths during the development; however, the proposed strength is 200 mg tablets which was studied in multiple clinical studies including the pivotal studies. The drug substance used in the proposed product is a mono-hydrobromide salt; however, the proposed strength is 200 mg of the free base.

The Applicant stated that there was no change in the tablet formulation throughout the clinical program and no change in formulation is proposed for the commercial product. The batches of the proposed drug product were manufactured at three different sites, with approximately (b) (4) batches at (b) (4) approximately (b) (4) batches at (b) (4), and approximately (b) (4) batches at Patheon. The commercial manufacturing site in Patheon Pharmaceuticals Inc. at Cincinnati, OH where clinical and the stability batches were manufactured.

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: During the IND stage, FDA had recommended the Applicant to provide a detailed dissolution method development report justifying the selection of the proposed dissolution method and acceptance criterion. The Applicant provided a detailed dissolution method development report in Module 3.2.P.2¹.

¹ [Application 211723 - Sequence 0001 - Tazemetostat Tablets Dissolution Method Development Report](#)

The Applicant’s proposed dissolution method and acceptance criterion are as following:

Table 1: Applicant’s proposed dissolution method and Acceptance Criterion

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	50 rpm
Volume	900 mL
Medium	0.1N HCl
Temperature	37.0 ± 0.5 C
Acceptance Criteria	NLT ^(b) ₍₄₎ % (Q) in 30 minutes

Drug Solubility: The Applicant stated that the solubility of the drug substance (salt form) was measured in pH 1.0, 2.0, 3.0, 4.0, 5.5, and 6.8 buffers after overnight agitation at 37°C according to the procedure described in the draft FDA Guidance for Industry, “Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System” (May 2015). Duplicate determinations at each pH were measured, with pH verified after addition of the drug substance to the buffer, using the traditional shake flask method. The solubility of the drug substance (salt) in the studied aqueous media as shown in Table 2.

Table 2: Drug Substance Solubility in Aqueous Media

Buffer Solution	Buffer pH	Solubility (mg/mL)
HCl/KCl (134 mM HCl)	1.0	7.27
HCl/KCl (13.4 mM HCl)	2.0	7.03
Acid phthalate 50 mM	3.0	6.87
Acid phthalate 50 mM	4.0	6.99
Neutralized phthalate 50 mM	5.5	0.508
Phosphate 50 mM	6.8	0.033

The Applicant also studied the solubility in simulated physiological fluids as summarized in the table below.

Table 3: Drug Substance Solubility in Simulated Physiological Fluids

Buffer Solution	Buffer pH	Solubility (mg/mL)
SGF	1.2	7.50
FeSSIF	5.0	3.83
FaSSIF	6.5	0.053

SGF = Simulated Gastric Fluid, FeSSIF = Fed State Simulated Intestinal Fluid, FaSSIF = Fasted State Simulated Intestinal Fluid

The Applicant's provided solubility data indicate that tazemetostat hydrobromide (HBr) has high solubility (7 mg/mL) in the pH range of 1-4 while the solubility decreases significantly at pH 5.5 and above (0.5 mg/mL in pH 5.5 buffer and 0.03 mg/mL in pH 6.8 buffer).

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

(b) (4)



² [Application 211723 - Sequence 0001 - Tazemetostat Tablets Dissolution Method Development Report; Table 7](#)

Discriminating Ability of the Dissolution Method: The Applicant tested the following parameters to evaluate the discriminating ability of the proposed dissolution method:

Formulation Variables

(b) (4)

Drug Substance Variables

Drug substance particle size

(b) (4)

Manufacturing Process Variables

(b) (4)

In the original submission, the Applicant did not clearly specify target values/levels of the critical attributes/variables tested for demonstrating the discriminating ability of the proposed dissolution method. The Applicant was requested to provide this information. Also, the Applicant was requested to provide the values/levels of these critical attributes/variables for the clinical/registration batches. The Applicant provided the requested information in the submission dated 09/05/2019.

The attributes/variables indicated in the Tazemetostat Tablets Dissolution Method Development Report (Module 3.2.P.2) that were varied to demonstrate discriminating ability of the proposed dissolution method are summarized in Table 8. The table includes the range tested, whether the method is discriminatory for that attribute/variable, and the target values/levels (acceptable range) for commercial batches. Table 9 shows the actual values/levels of relevant attributes/variables for batches that were used in the pivotal clinical efficacy study EZH-202, and the batches that were used for primary (registration) and supportive stability studies.

Table 8: Summary of Attributes used to Define Discriminating Ability of the Dissolution Method

Attribute/Variable	Range Tested in Dissolution Report	Discriminating Ability Disso Method?	Target/Acceptable Range Commercial Batches
(b) (4)			

Table 9: Summary of Relevant Attributes for Batches used in the Clinical Efficacy Study, Primary, and Supportive Stability Studies

DP Batch	Use ^a	DS Particle Size, D90 (µm)	(b) (4)
P48028AZA	C		(b) (4)
P48034AZA	C		
P55016AZA	C		
P55019AZA	C		
16A019	C		
16A021	C		
16B068	C		
16D149	C		
16E182	C		
16H245	C		
17B037	C		
3155655R	C, S		
3160196R	R		
3163540R	C		
3163636R	R		
3165225R	R		
3164121R	S		
3164124R	C		

a C: Clinical efficacy study EZH-202. R: Registration (primary) stability, S: supportive stability
b (b) (4)

The results of individual discriminating ability studies towards critical formulation variables, critical material attributes and critical process parameters are described below.

Formulation Variables

(b) (4)

(b) (4)



Drug Substance

Drug Substance Particle Size

The effect of drug substance particle size was evaluated with respect to the impact on the dissolution profiles of the drug product. Table 16 shows the particle size distribution for the drug substance batches and the corresponding drug product batches test for the effect on dissolution. The results are shown in Table 17 and Figure 4.

Table 16: Drug Substance Particle Size Distribution for Each Drug Product Lot

Lot No.	DS Lot #	Particle Size of Drug Substance		
		D90 (µm)	D50 (µm)	D10 (µm)
1642-5298	80029756D			
1642-5302	80029756D Cut 2			
1642-5304	80029756D Cut 1			

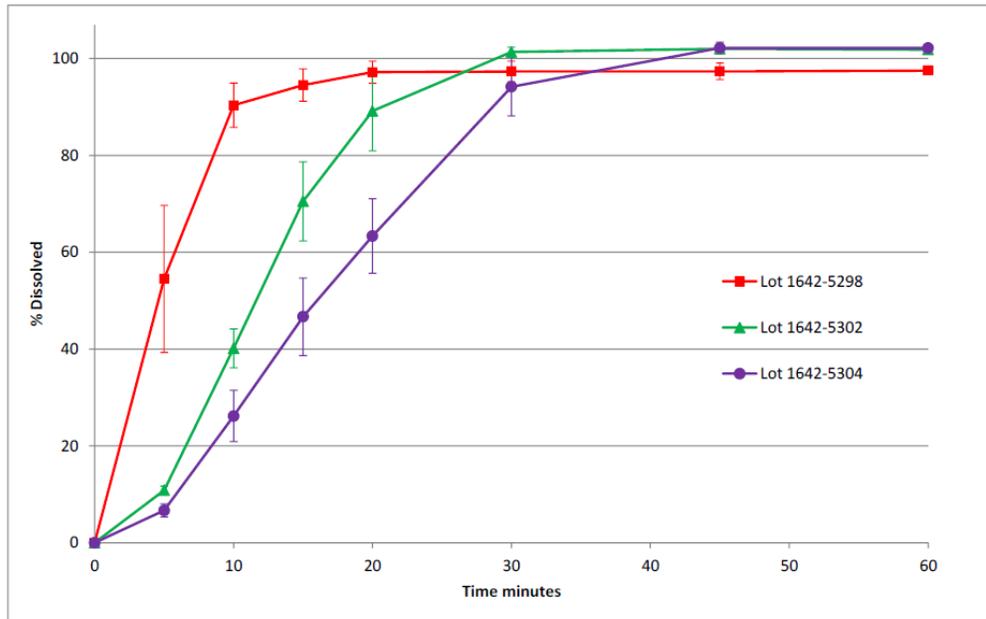
(b) (4)

Table 17: Effect of Drug Substance Particle Size on Dissolution Profiles

Lot No.	Time (minutes)	Average %Dissolved	Minimum %Dissolved	Maximum %Dissolved	%RSD
Lot 1642-5298	5	55	(b) (4)	(b) (4)	34
	10	90			6
	15	96			3
	20	97			3
	30	97			3
	45	97			2
	60	98			3
	75	98			3
Lot 1642-5302	5	11			8.5
	10	40			12.1
	15	71			13.9
	20	89			11.3
	30	101			1.2
	45	102			0.5
	60	102			0.5
	75	102			0.5
Lot 1642-5304	5	7			27.3
	10	26			25.4
	15	47			20.6
	20	63			14.8
	30	94			7.6
	45	102			1.5
	60	102			1.5
	75	102			1.5

900 mL 0.1N HCL, Apparatus II (Paddles) at 50 rpm References: CRT-00657, RPT-00027

Figure 4: Dissolution Comparison Based on Particle Size Distribution of the Active



Reviewer's Assessment:

OPQ-XOPQ-TEM-0001v06

Page 112

Effective Date: February 1, 2019

(b) (4)

The three tested lots are different from in each in terms of their dissolution, with f2 value being lower than 50. This indicated that the proposed dissolution method is discriminating towards the drug substance particle size distribution at the studied levels. However, it is noted that all three batches show nearly complete dissolution by 30 minutes, and the proposed product has Tmax of in the range of 1-2 hour. Therefore, the difference in dissolution trend during first 30 minutes may not have clinical implications. From a biopharmaceutics perspective, there is no concern regarding the proposed drug substance particle size specification of D90= (b) (4) μm .

(b) (4)

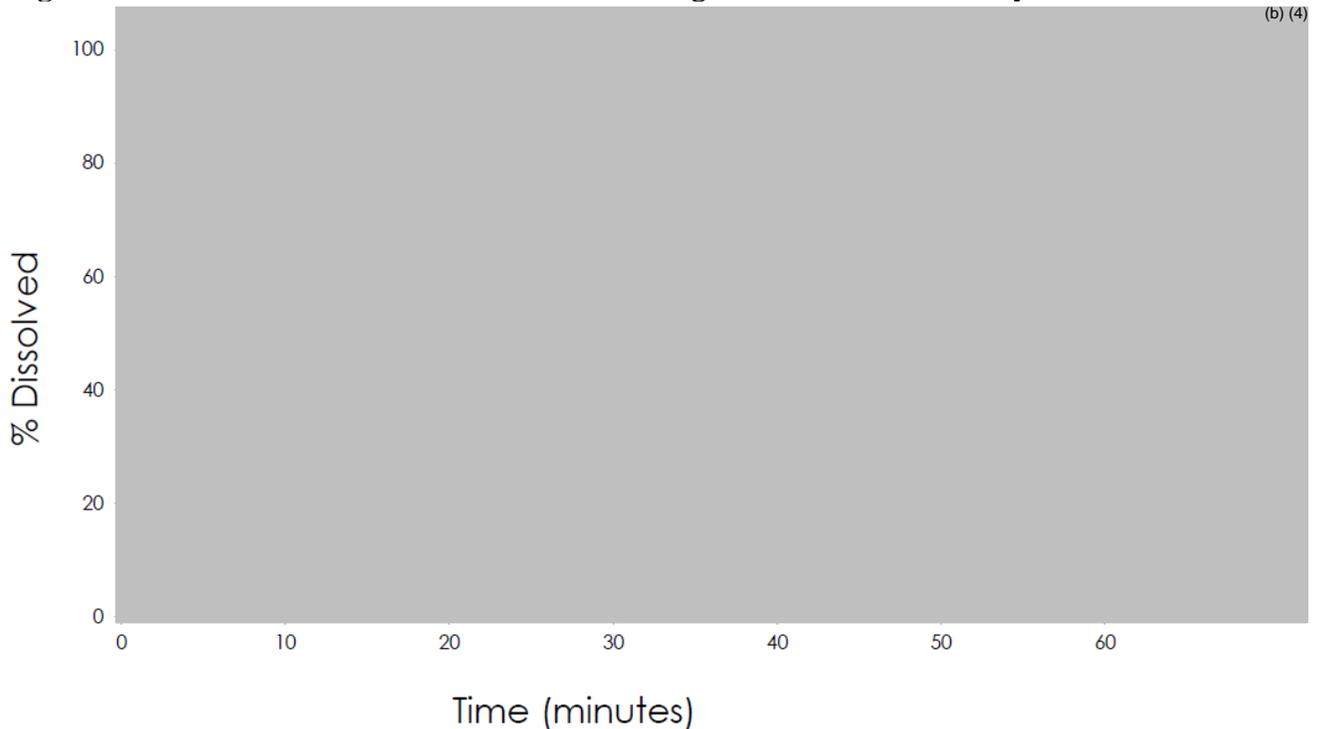
Reviewer's Assessment:

(b) (4)

The totality of the provided information/data indicate that the proposed dissolution method is appropriately selected and is discriminatory towards several critical attributes/variables. Therefore, the proposed dissolution method is deemed **adequate** for quality control testing of the proposed product.

Dissolution Acceptance Criterion: As per the current practice at the FDA, dissolution acceptance criterion is set based on the dissolution profiles of the clinical batch(es) at the time of release. Also, it is expected that the dissolution profiles do not differ significantly between the clinical and registration batches and during the stability testing period. In the original submission, the Applicant did not provide full profile dissolution data for clinical and registration batches. Therefore, the Applicant was requested to provide these data. In response (dated 09/05/2019), the Applicant provided the requested dissolution data.

Figure 11 summarizes the full dissolution profiles of the 13 drug product lots used in the pivotal efficacy study.

Figure 11: Dissolution Profiles for Tazemetostat Drug Product used in Efficacy Studies

The Applicant's proposed dissolution acceptance criterion of 'NLT $\frac{(b)}{(4)}\%$ (Q) at 30 minutes' is based on the dissolution data from the clinical batches. Also, the data from the discriminating ability studies indicate that the proposed dissolution method with dissolution acceptance criterion of 'NLT $\frac{(b)}{(4)}\%$ (Q) at 30 minutes' is likely to identify deviation in the product's quality. Based on the provided information/data, the proposed dissolution acceptance criterion is deemed 'adequate' for quality control testing of the proposed product.

The FDA approved dissolution method and acceptance criterion for the proposed product are described in Table 1.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the pivotal clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

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/

OLEN M STEPHENS

10/18/2019 09:46:46 AM

the primary reviews herein were already filed in Panorama. This is simply a compilation of the OPQ chapter reviews.