CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215413Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 215413
Assessment #1

Drug Product Name	TRIUMEQ PD (abacavir, dolutegravir, and lamivudine)
Dosage Form	Tablets for Oral Suspension
Strength	60 mg/5 mg/30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ViiV Healthcare Company
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD1 (eCTD 0001)	09/30/2021	Drug Substance, Drug Product, OPMA, Biopharmaceutics, Labeling, EA Team
SD3 (eCTD 0003)	11/15/2021	Drug Substance, OPMA, Biopharmaceutics
SD4 (eCTD 0004)	01/14/2022	Drug Product, OPMA, Biopharmaceutics
SD6 (eCTD 0005)	02/04/2022	OPMA
SD7 (eCTD 0007)	02/15/2022	Drug Product
SD8 (eCTD 0008)	02/22/2022	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	
Drug Product & Labeling	Hailin (Sheena) Wang	David Claffey
Manufacturing	Brijeshkumar Vaghasia	Bo Jiang
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks and Erica Keafer	
Application Technical Lead	Hailin (Sheena) Wang	
Environmental	Hailin (Sheena) Wang	David Claffey
Labeling		

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	IV	(b) (4)		N/A		
	III			N/A		Refer to container closure assessment in the DP review
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		

N/A: All DMFs have been reviewed previously for other products and found adequate. And there is sufficient information in the current application. Therefore, the updated DMFs did not need to be reviewed during the current review cycle.

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

Document	Application Number	Description
NDA submission for Ziagen Tablets	NDA 020977	CMC cross-reference for abacavir sulfate DS
NDA submission for Epivir tablets	NDA 020564	CMC cross-reference for lamivudine DS
NDA submission for Tivicay Tablets	NDA 204790	CMC cross-reference for dolutegravir sodium DS

Refer to section 1.4.4. in SD1 for full list of cross-referenced IND and NDA which incorporates historical clinical data of the three actives.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor

Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other				

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on February 09, 2022. Therefore, this NDA is recommended for APPROVAL by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

TRIUMEQ PD tablets for oral suspension is a new pediatric dosage form developed to expand the use of the TRIUMEQ (approved under NDA 205551 on 08/22/2014) to pediatric patients weighing at least 10 kg (originally proposed 14 kg to <25 kg). Prior knowledge of the existing single, double, or triple components tablet products developed by ViiV regarding drug-drug and drug-excipients compatibility as well as stability of APIs, has been used throughout the design and development of TRIUMEQ PD tablets.

TRIUMEQ PD tablets is a fixed dose combination product containing the same three active ingredients. It is prepared as immediate release (b) (4) dispersible tablet for administration as oral suspension upon mixing with drinking water. Each tablet contains 70.2 mg abacavir sulfate which is equivalent to 60 mg abacavir free base, 5.26 mg dolutegravir sodium which is equivalent to 5 mg dolutegravir free acid, and 30 mg of lamivudine, which is 10 times lower in strength for each component as compared to the approved TRIUMEQ tablets.

Proposed Indication(s) including Intended Patient Population	Complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 10 kg
Duration of Treatment	Chronic treatment
Maximum Daily Dose	
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The Applicant cross-referenced the CMC information for the three drug substances to three respective NDAs: NDA 020977 ZIAGEN tablets for abacavir sulfate; NDA 020564 EPIVIR tablets for lamivudine; NDA 204790 TIVICAY tablets for dolutegravir sodium. The content of the three NDAs is adequate to support NDA 215413

For each of the three drug substances, batch data for drug substance batches used to manufacture drug product primary stability batches and the current drug substance specifications were provided in NDA 215413 and found adequate.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the review by Katherine Windsor, Ph.D.

Drug Product: Adequate

TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) Tablets for Oral Suspension, 60mg/5mg/30mg, are yellow, capsule-shaped, strawberry cream flavored, biconvex, film coated tablets debossed with "SV WTU" on one side. (b) (4) (b) (4) All excipients used for preparation of the dispersible tablets except for the strawberry flavor and film coating which are controlled per in-house specification.

The Triumeq PD tablets are supplied in 90-count in HDPE bottles with a (b) (4) (b) (4) desiccant canister and closed with a child-resistant closure, which is further co-packaged with a dosing cup in a convenience kit.

Three primary DP batches were manufactured at production scale (b) (4) with three different drug substance lots for each API. The proposed shelf life of 36 months at storage below 30°C is adequately supported by 24 months of long term and 6 months accelerated stability batch results along with 30 days or 90 days in-use stability data. In-use compatibility and dose delivery studies support the 30 mins in-use time after mixing with water and complete cumulative dose delivery of the suspension with the dosing cup following instructions described in the IFU.

The claim of categorical exclusion was evaluated in the drug product review, and found acceptable.

Certain information from the approved TRIUMEQ, TIVICAY PD and DOVATO submissions provided additional support for the unique impurity

control strategy (at stability only) and reduced schedule testing in the post approval stability protocol for commercial manufacturing.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to Dr. Sheena (Hailin) Wang, Drug Substance review in the IQA Chapters below.

Labeling: Adequate

Labeling recommendations were communicated to the OND project manager. The labeling was found adequate.

Manufacturing: Adequate

(b) (4)

Biopharmaceutics: Adequate

The dissolution method and acceptance criteria of NLT (b) (4) (Q) at 60 minutes for dolutegravir and NLT (b) (4) (Q) at 15 minutes for Abacavir and Lamivudine was found acceptable as a quality control (QC) test for the proposed drug product.

The need for bridging between the clinical batch drug product used in relative bioavailability study 205894 and the proposed commercial drug product (also used in the food effect study 216149) was also evaluated due to minor differences in manufacturing process, tablet coat weight gain and suspension solids weight as well as debossing. The comparable dissolution profiles between the clinical and proposed commercial product demonstrated that these minor differences had no impact on dissolution and are therefore not expected to have an impact on the drug product quality and in vivo performance. In addition, there is no change in the drug substance and/or drug product manufacturing process and manufacturing site between the clinical batches and the primary stability batches (commercial product). The data and information available in the current submission is sufficient to support the comparability between clinical batch and proposed commercial product. No additional in vitro or in vivo bridging studies are needed.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details refer to Dr.Mei Ou's Biopharmaceutics review in the IQA Chapters below.

C. Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Assay, stability	6	Drug-excipient, drug-drug compatibility demonstrated in Triumeq tablets.		Assay results of stability samples meet stability specification. No trend observed during stability. Disproportionation of dolutegravir sodium to free acid is not observed in primary stability batches.
Physical stability (solid state)	36 (DTG)	DTG (BCS II) (b) (4) is shown to be a stable polymorph in Triumeq tablets that has the same DTG (b) (4) composition.		Dolutegravir (BCS II) (b) (4) has been shown to be a stable polymorph in Triumeq tablets which is formulated in the same DTG (b) (4) composition. Solid state form of abacavir and lamivudine has minimal impact on dissolution as both drug substances are highly soluble in water.
	24	abacavir sulfate is (b) (4) and BCS III		
	24	lamivudine is (b) (4) crystalline (b) (4) and BCS III		

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Content uniformity	48	(b) (4)		Content uniformity test by weight variation is included in the DP specification.
Microbial limits	6	Microbial limits tested in the DP specification		Defer to process reviewer
Dissolution	32 (DTG)	The applicant describes DTG as a BCS class 2 compound		Defer to biopharm reviewer
	12	ABC and 3TC as BCS class 3 compound		

D. List of Deficiencies: None

Application Technical Lead Name and Date: Hailin (Sheena) Wang, Ph.D. 03/01/2022

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 215413-ORIG-1 [505(b)(1)]
Drug Product Name/Strength: TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) Tablets for Oral Suspension, 60/5/30 mg
Route of Administration: Oral
Proposed Indication: Treatment of HIV infection for pediatric patients weighing between 14 and 25 kg
Applicant Name: ViiV Healthcare Company
Submission Dates: 09/30/2021 (original), 11/15/2021 (response to Biopharmaceutics IR), 01/14/2022 (response to Biopharmaceutics IR)
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, Triumeq PD (abacavir, dolutegravir, and lamivudine) Tablets for Oral Suspension (known as dispersible tablets, DT), 60/5/30 mg, is indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 14 kg to less than 25 kg. The Applicant of NDA 215413 owns an approved drug product, Triumeq (abacavir, dolutegravir, and lamivudine) Tablets, 600/50/300 mg, which is indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 40 kg (NDA 205551, approved on 08/22/2014). The Applicant is relying, in part, on previously submitted pharmacokinetics, safety and efficacy data for each drug substance and the relative bioavailability data from Study 205894 between Triumeq PD, 60/5/30 mg, and Triumeq (abacavir, dolutegravir, and lamivudine) Tablets, 600/50/300 mg, and the food effect data from Study 216149 (both studies in healthy adults) to support the revised dosing recommendations for the approved Triumeq Tablets (submitted as NDA 205551/S-28) and the currently proposed Triumeq PD Tablets (NDA 215413) for Oral Suspension in pediatric patients weighing $\geq$ 14 kg but $\leq$ 25 kg.

In the current NDA 215413, the Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion(a) as a quality control (QC) test for the proposed drug product, (ii) the need for bridging.

In Vitro Dissolution Testing of the Finished Product:
The following proposed dissolution method and acceptance criteria are considered acceptable as a quality control (QC) test for the proposed drug product, Triumeq PD (abacavir, dolutegravir, and lamivudine) Tablets for Oral Suspension, 60/5/30 mg.

Dissolution Method	USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.01 M phosphate buffer with 0.5 mM EDTA, pH 6.8, 37°C (*Note: One whole tablet is placed into each vessel to conduct the dissolution test instead of using the suspension as the dissolution sample*)
Acceptance Criteria	Dolutegravir: Q= (b) (4) at 60 minutes Abacavir and Lamivudine: Q (b) (4)% at 15 minutes

Bridging:
The clinical batch used in the relative bioavailability study 205894 and the proposed commercial drug product (also used in the food effect study 216149) have the same qualitative and quantitative composition but have minor differences in (i) manufacturing process, (ii) tablet coat weight gain and suspension solids weight, (iii) the image (a plain image for the clinical tablets vs. a debossed image for the commercial tablets). The comparable dissolution profiles between the clinical and commercial batches demonstrated that these minor differences had no impact on dissolution and are therefore not expected to have an impact on the drug product quality and in vivo performance. There is no change in the drug substance and/or drug product manufacturing process and manufacturing site between the clinical batches and the primary stability batches. Therefore, no additional in vitro or in vivo bridging studies are needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 215413 for the proposed drug product, TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) Tablets for Oral Suspension, 60/5/30 mg, is recommended for **APPROVAL.**

BIOPHARMACEUTICS REVIEW

The proposed drug product, Triumeq PD (abacavir, dolutegravir, and lamivudine, ABC/DTG/3TC) Tablets for Oral Suspension, 60/5/30 mg, are yellow, capsule shaped, biconvex, film-coated fixed-dose combination (b) (4) tablets for oral suspension debossed with "SV WTU" on one face. (b) (4)

The tablets are designed to be dispersed in a small amount of water to form a suspension prior to administration. The tablet has also been designed to be directly taken by mouth without dispersing in water. The deboss is designed to aid tablet identification and the tablets are coated with a (b) (4) yellow film coat. The composition of the proposed drug product is presented in Table 1 below.

Table 1: The composition of the proposed Triumeq PD (ABC/DTG/3TC) Tablets for Oral Suspension, 60/5/30 mg
(*from M.3.2.P.1*)

Component	Quantity (mg/tablet)	Function	Reference to Standard[5]
(b) (4)			

1. Physicochemical characteristics of the drug substances

The Applicant stated that the drug substances Abacavir (ABC) and Lamivudine (3TC) are BCS III compounds, and Dolutegravir (DTG) is a BCS II compound. The solubility data of drug substances are summarized in Table 2 below. Note that a BCS designation was not requested, nor required.

Table 2: Physicochemical Characteristics of Abacavir, Dolutegravir, and Lamivudine (*summarized from M.3.2.P.2*)

Abacavir (ABC)	Dolutegravir (DTG)	Lamivudine (3TC)
High solubility: pH 1.6, 110 mg/mL pH 12.2, 22 mg/mL Water, 77 mg/mL	*Low solubility:* (b) (4) Dolutegravir Sodium: pH 1.2, 0.021 mg/mL pH 5.0, 0.170 mg/mL pH 6.5, 0.239 mg/mL pH 7, 0.323 mg/mL pH 8, 1.05 mg/mL pH 9, 3.9 mg/mL Water, 3.176 mg/mL	*High solubility:* pH 1.2, 145.8 mg/mL pH 4.5, 169.7 mg/mL pH 6.8, 75.7 mg/mL Water, 98.1 mg/mL
	(b) (4)	
Low permeability: Papp of 36.5 nm/s (36.5 x 10^{-6} cm/s) in MDCK cells	*High permeability:* P7.4[abs] value of 253 nm/s P5.5[abs] value of 265 nm/s	*Low permeability:* Papp of 19 nm/s (1.9 x 10^{-6} cm/s) in Caco-2 cells
(b) (4)		

2. In vitro dissolution method and acceptance criterion

The proposed dissolution method and acceptance criteria for the proposed drug product (Triumeq PD Tablets for Oral Suspension, 60/5/30 mg), and the previously approved dissolution method and acceptance criteria for the previously approved drug product (Triumeq Tablets, 600/50/300 mg, under NDA 205551) are summarized in Table 3 below.

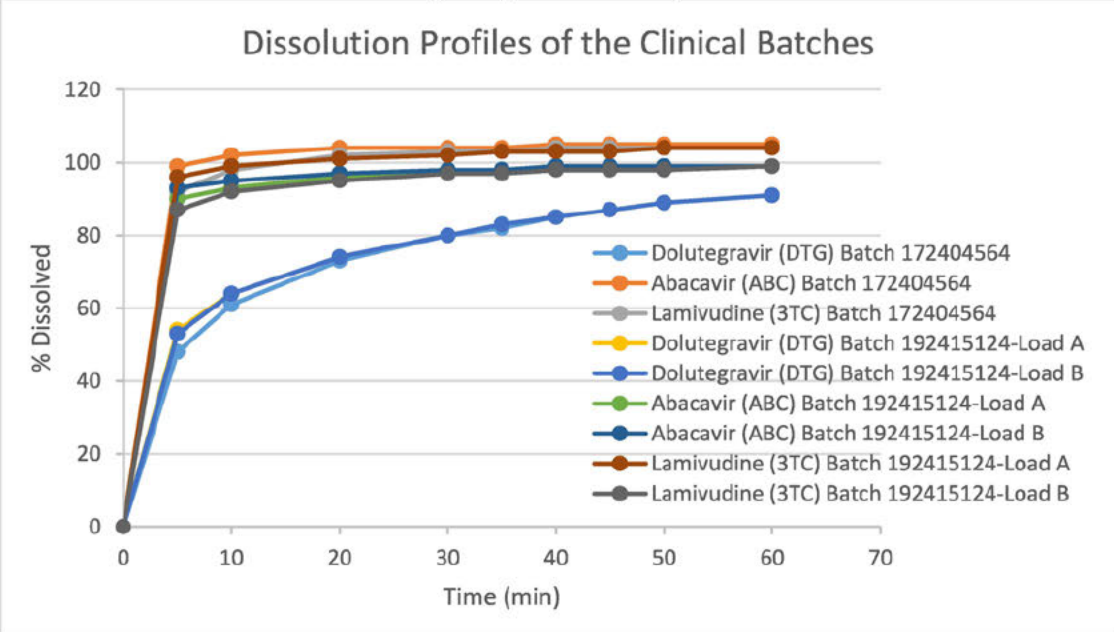
Table 3: The dissolution methods and acceptance criteria for the proposed drug product (Triumeq PD Tablets for Oral Suspension, 60/5/30 mg), and the previously approved dissolution method and acceptance criteria for the previously approved drug product (Triumeq Tablets, 600/50/300 mg, under NDA 205551)
(*from M.3.2.P.5.2 and M.3.2.P.5.3*)

	For the proposed drug product (Triumeq Tablets for oral suspension, current NDA 215413)	**For the approved drug product[1] (Triumeq Tablets, NDA 205551)**
Dissolution Method	USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.01 M phosphate buffer with 0.5 mM EDTA, pH 6.8, 37°C	USP Apparatus II (Paddle), 85 rpm, 900 mL of 0.01 M phosphate buffer with 0.5% SDS, pH 6.8, 37°C
Acceptance Criteria	Dolutegravir: Q= (b)(4)% at 60 minutes Abacavir and Lamivudine: Q= (b)(4)% at 15 minutes	Dolutegravir: Q= (b)(4)% at 35 minutes Abacavir and Lamivudine: Q= (b)(4)% at 30 minutes

Note that the dissolution test is performed on the whole tablet (one tablet per vessel) and not on the suspension (*see M.3.2.P.5.2*).

The dissolution profiles of the pivotal clinical batches containing the commercial formulation (Batch 172404564 from Clinical Study 205894, Batch 192415124 from Clinical Study 216149) generated by the proposed dissolution method are plotted by this Reviewer and presented in Figure 1 and Table 4 below.

Figure 1: Mean dissolution profiles of the proposed Triumeq PD Tablets for Oral Suspension, 60/5/30 mg, generated by using the proposed dissolution method
(*data from M.2.7.1*)



[1] Biopharmaceutics Reviews for NDA 205551-ORIG-1 and SUPPL-6:
https://panorama.fda.gov/project/view?ID=57c9bf5601520f738f4e0f7c0eaf43df

Table 4: Dissolution data of the proposed Triumeq PD Tablets for Oral Suspension, 60/5/30 mg, generated by using the proposed dissolution method (*data from M.2.7.1*)

Study	Drug Product Batch No.	Dosage Form	Conditions	No. of Dosage Units	Mean % Dissolved (range)			
200402	162395634	DTG/ABC/3TC Dispersible Tablets, 10 mg/150 mg/75 mg	NA	NA	NT			
205894	172404564	DTG/ABC/3TC Dispersible Tablets, 5 mg/60 mg/30 mg	Dissolution Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium: Phosphate Buffer, pH6.8 with 0.5mM EDTA Medium volume: 900 mL Temperature: 37°C Clinical release criteria: Q= (b) (4) at 60 min for DTG, ABC and 3TC	12[a]	Collection times (mins)	DTG	ABC	3TC
					5	(b) (4)		
					10			
					20			
					30			
					35			
					40			
					45			
					50			
					60			

Study	Drug Product Batch No.	Dosage Form	Conditions	No. of Dosage Units	Mean % Dissolved (range)					
216149 (Cohort 1)	192415124	DTG/ABC/3TC Dispersible Tablets, 5 mg/60 mg/30 mg	Dissolution Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium: Phosphate Buffer, pH6.8 with 0.5mM EDTA Medium volume: 900 mL Temperature: 37°C Clinical release criteria: Q= (b) (4) at 60 min for DTG, ABC and 3TC	12[a]	Collection times (mins)	DTG		ABC		3TC	
					-	Load A	Load B	Load A	Load B	Load A	Load B
					5	(b) (4)					
					10						
					20						
					30						
					35						
					40						
					45						
					50						
					60						

Notes:
NA = Not Applicable; NT=Not Tested
a. Dissolution data was generated post-release according to the method in m3.2.P.5.2 Analytical Procedures as this test was not part of the specification at the time of manufacture.
b. Batch of tablets was coated in two coating loads, Load A and Load B. 6 dosage units were tested for each coating load.

The stability data of three registration batches (batch R860949, R860951, and R860952) show that Abacavir (ABC) and Lamivudine (3TC) exhibited (b) (4)% dissolution in both 15 minutes and 20 minutes after storage for up to 18 months under long-term and accelerated stability conditions (*data are provided in M.3.2.P.8.3*). Dolutegravir exhibited (b) (4)% dissolution at the 60 minutes time point after storage for up to 24 months under long-term and accelerated stability conditions (*data are provided in M.3.2.P.8.3*). No trends of dissolution were observed during stability testing for the three stability batches.

Since there is no dissolution method development report submitted, the 1st Biopharmaceutics Information Request (IR) was conveyed on 11/09/2021 (*see Biopharmaceutics Information Requests in Appendix 1*), requesting additional solubility data of dolutegravir in the dissolution medium and justification of selecting the proposed dissolution medium[2].

In the 11/15/2021 response to the Biopharmaceutics 1st IR, the solubility of dolutegravir in the dissolution medium, 0.01 M phosphate buffer pH 6.8 with 0.5 mM EDTA, at 37°C, was reported as 0.03 mg/mL. Therefore, sink condition for dolutegravir (solubility > 5 mg x 3/900 mL = 0.017 mg/mL) is achieved in the proposed dissolution medium.

The Applicant explained that the use of 0.5 mM EDTA in 0.01 M phosphate buffer pH 6.8 is to (b) (4) . The use of 0.5 mM EDTA is also supported by prior knowledge from a previously approved drug product, Tivicay PD (NDA 213983, owned by the same Applicant). Note that the use of 0.5 mM EDTA (b) (4) was found acceptable for the dissolution testing of Tivicay PD[3]. Furthermore, since the proposed drug product is considered low strength (i.e., abacavir/dolutegravir/lamivudine are 60/5/30 mg), the addition of sodium dodecyl sulfate (SDS) to the dissolution medium is not necessary. The dissolution methods and acceptance criteria are summarized as below (Table 5):

[2] NDA 215413 Information Request dated 11/09/2021: https://panorama.fda.gov/internal/document/preview?versionID=618a92350021095dd8338b11e01b341f&ID=618a91a8004d6c1af042fdaf53e1ea91

[3] NDA 213983-ORIG-1, Biopharmaceutics Review, dated 05/11/2020: https://panorama.fda.gov/internal/document/preview?versionID=5eb95300005f2297acaef46cd2e493e7&ID=5ea2c9ad00328ecc6c2169a27d31b01b

Table 5: The dissolution method and acceptance criteria for the proposed drug product (Triumeq PD Tablets for Oral Suspension, 60/5/30 mg), and the previously approved dissolution methods and acceptance criteria for the previously approved drug products (Triumeq Tablets, 600/50/300 mg, under NDA 205551; and Tivicay PD, 5 mg, under NDA 213983)

	For the proposed Triumeq PD Tablets for Oral Suspension (current NDA 215413)	**For the approved Triumeq Tablets (NDA 205551)**	**For the approved Tivicay PD Tablets (NDA 213983)**
Dissolution Method	USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.01 M phosphate buffer with 0.5 mM EDTA, pH 6.8, 37°C	USP Apparatus II (Paddle), 85 rpm, 900 mL of 0.01 M phosphate buffer with 0.5% SDS, pH 6.8, 37°C	USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.01 M phosphate buffer with 0.5 mM EDTA, pH 6.8, 37°C
Acceptance Criteria	Dolutegravir: Q(b) (4)% at 60 minutes Abacavir and Lamivudine: Q(b) (4)% at 15 minutes	Dolutegravir: Q(b) (4)% at 35 minutes Abacavir and Lamivudine: Q(b) (4)% at 30 minutes	Dolutegravir: Q(b) (4)% at 25 minutes

Overall, the proposed dissolution method and acceptance criteria for the proposed Triumeq PD Tablets for Oral Suspension, 60/5/30 mg, are found acceptable because:

- Dolutegravir can reach sink condition in the proposed dissolution medium.
- The justification of using 0.5 mM EDTA in dissolution medium is acceptable.
- The selection of 50 rpm paddle speed is appropriate when both paddle speeds (50 rpm (b) (4) showed similar low variability with marginal difference in % dolutegravir release.
- Per the proposed labeling section 2.4, either the whole tablet or the oral suspension (by dispersing the whole tablet into water) can be given to the patients. Therefore, it is acceptable that the whole tablet (instead of the suspension) is used as the dissolution sample (placing one whole tablet into dissolution vessel).
- Based on the dissolution data in Table 4 above, a dissolution acceptance criterion of Q(b) (4)% at (b) (4) for dolutegravir would require Stage 2 or 3 testing for the clinical drug product batch. However, the proposed dissolution acceptance criterion of Q(b) (4)% at 60 minutes for dolutegravir will pass the clinical batch at Stage 1. Therefore, the proposed dissolution acceptance criterion of Q(b) (4)% at 60 minutes for dolutegravir is acceptable. The totality of the information and dissolution data support the proposed dissolution acceptance criteria for dolutegravir (Q(b) (4)% at 60 minutes), abacavir (Q(b) (4)% at 15 minutes), and lamivudine (Q(b) (4)% at 15 minutes).

3. Bridging

The clinical batch used in the relative bioavailability study 205894 and the commercial batch used in the food effect study 216149 have the same qualitative and quantitative composition but have minor difference in (i) manufacturing process, (ii) tablet coat

weight gain and suspension solids weight, (iii) image (the plain image in clinical tablets vs. the debossed image in commercial tablets) (as described in page 6 of M.2.7.1 and Table 72 in M.3.2.P.2.3). To support the above changes, comparative dissolution profile data between the clinical and the commercial batches, obtained by using the proposed dissolution method, were requested (*see Biopharmaceutics IR dated 12/20/2021 in Appendix 1*).

In the response submitted on 01/14/2022, the Applicant provided the comparative dissolution profile data of the clinical batch (batch # 172404564) and the commercial batch (batch # 192415124/R871160), obtained by using the propose dissolution method. See Table 6 and Figures 2 to 4 below. The comparative dissolution profiles for abacavir and lamivudine showed similar dissolution profiles with (b) (4)% dissolution at 15 minutes. The similarity factor (*f2*) for the dolutegravir dissolution profiles of the clinical and commercial batches is 78, indicating that the profiles are similar.

Table 6: Batch information
(*from 01/14/2022 submission*)

Study	Formulation	Batch Number	Manufacture Date	Date of Dissolution Testing	Storage Condition prior to Dissolution Testing
RBA (205894)	Clinical	172404564	November 2017	May 2019	Controlled room temperature
Food Effect (216149)	Commercial	192415124 (R871160)	June 2019	October 2019	Controlled room temperature

Figure 2: Mean Dolutegravir Dissolution Profiles for DTG/ABC/3TC Dispersible Tablets
(*from 01/14/2022 submission*)

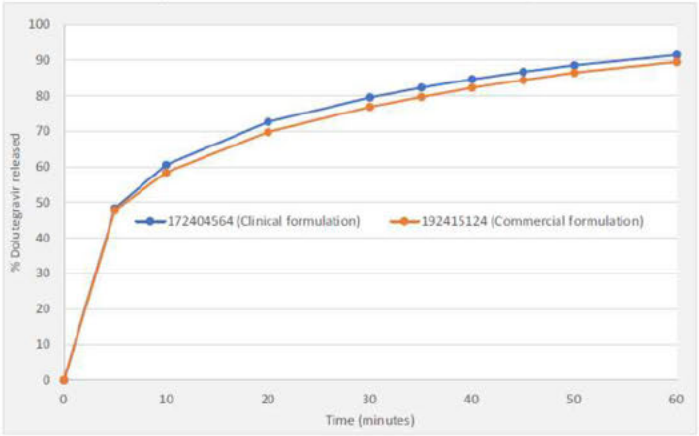


Figure 3: Mean Abacavir Dissolution Profiles for DTG/ABC/3TC Dispersible Tablets (*from 01/14/2022 submission*)

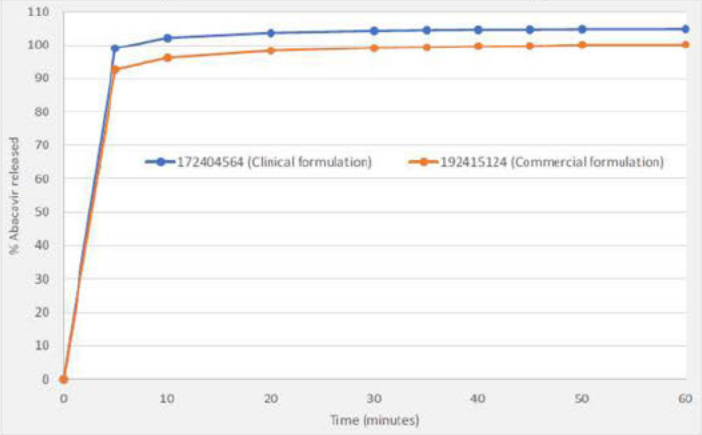
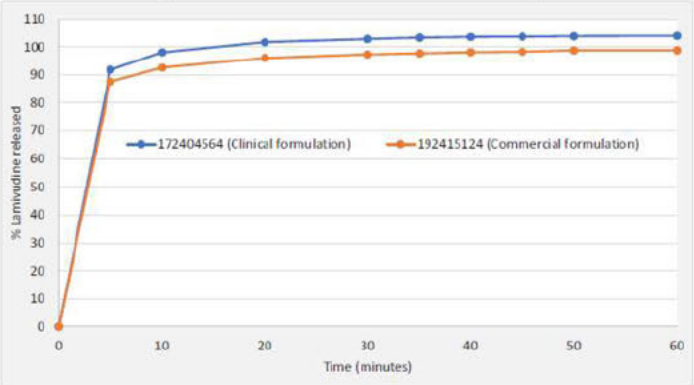


Figure 4: Mean Lamivudine Dissolution Profiles for DTG/ABC/3TC Dispersible Tablets (*from 01/14/2022 submission*)



Therefore, the comparable dissolution profile data between the clinical drug product and the commercial drug product demonstrated that the above minor differences in drug product manufacturing process, tablet coat weight gain and suspension solids weight, and tablet imaging had no impact on dissolution, and are therefore not expected to have impact on product quality and in vivo performance. There is no change in the drug substance and/or drug product manufacturing process and manufacturing site between the clinical drug product and the commercial drug product. Therefore, no additional in vitro or in vivo bridging studies are needed.

APPENDIX 1
BIOPHARMACEUTICS INFORMATION REQUESTS AND APPLICANT'S RESPONSES

Biopharmaceutics 1st IR (conveyed on 11/09/2021):

In order to facility the review, please provide:

(1) the solubility data of dolutegravir in dissolution medium at 37°C
(2) the justification of selecting the proposed dissolution method conditions including the use of 0.5 mM EDTA

Applicant's Responses to 1st IR (submitted on 11/15/2021):
\\CDSESUB1\evsprod\nda215413\0003\m1\us\111-information-amendments\cmc-response-15nov2021.pdf

Biopharmaceutics 2nd IR (conveyed on 12/20/2021):

To support the changes (i.e., coat weight gain, suspension solids, and deboss image) between the clinical formulation used in BA Study 205894 and Food Effect Study 216149, and the commercial formulation, provide comparative dissolution profile data (raw data, mean, RSD, full profiles/figures, *f2* calculation, n=12), using the currently proposed dissolution method (USP Apparatus II Paddle, 50 rpm, 900 mL of 0.01 M phosphate buffer with 0.5 mM EDTA, pH 6.8, 37°C). In your response, provide detailed batch information, such as drug product batch number, date the batch was manufactured, age of the batch at the time of dissolution testing, storage conditions, etc.

Applicant's Responses to 2nd IR (submitted on 01/14/2022):
\\CDSESUB1\evsprod\nda215413\0004\m1\us\111-information-amendments\cmc-response-14jan2022.pdf

Mei Ou

Digitally signed by Mei Ou
Date: 1/31/2022 02:07:31PM
GUID: 54ca9d7000073c57d2eb7cc6e42c05bb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 1/31/2022 03:08:54PM
GUID: 50743ccc000031928b54eba1769a5df9

CHAPTER IV: LABELING

NDA 215413

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (as in SD14 on 08/05/21)

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).	Adequate	Strengths are based on the active moiety of the salt drug substances.

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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 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)	Adequate	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	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 11).	N/A	
For radioactive products, include radiation dosimetry	N/A	

for the patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

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	Description includes color, shape, flavor, film-coating and debossing.
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	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

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)	Adequate	
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)"	Adequate	**Recommended revision communicated to OND:** Revised the equivalency statements for DP containing salt DS: "(present as 70.2 mg of abacavir sulfate), and "(present as 5.26 mg of dolutegravir sodium)". (b) (4) is used here per branch chief Dr. David Claffey's recommendation.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	**Recommended revision communicated to OND:** Revised the inactive ingredients for tablet film-coating to follow 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	Chemical name and structural formula are consistent with information provided in section 3.2.S.1.
If radioactive, statement of important nuclear characteristics.	N/A	

Other important chemical or physical properties (such as pKa or pH)	Adequate	DS solubility properties is consistent with information provided in section 3.2.S.1.

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")	Adequate	**Recommended revision communicated to OND:** Deleted fanciful proprietary names for an inactive ingredient (tablet film-coating) [see 21 CFR 201.10(c)(3)]
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)

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)	Adequate	
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	

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

disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	**Recommended revision communicated to OND:** Although stability data support the storage below 30°C, the storage statement is revised to uniform storage statement per OPQ recommendation "Store at 20°C to 25°C excursion permitted between 15°C and 30°C (59°F to 86°F). [See USP Controlled Room Temperature].", which is also consistent with the storage statement for the approved adult tablets.
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	Adequate	

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

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	

2.0 PATIENT LABELING

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Patient Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	In-use condition and time is supported by data
Storage and handling information (if applicable)	Adequate	**Recommended revision communicated to OND:** The storage statement in the IFU should be revised to the uniform storage statement to be consistent with recommendation provided in the PI.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	Desiccant is in a canister that's readily distinguished from the tablets.
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

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

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (taken from SD1 on 09/30/2021)

(b) (4)

3.2 Carton Labeling (taken from SD1 on 09/30/2021)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence (21 CFR 201.10(g)(2))	Adequate	The font of the established name appears to be at least half as large as the letters comprising the proprietary name. The propriety name and established name appear to have same prominence.
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.	Adequate	Equivalency statement provided for the salt drug substances
Net contents ((21 CFR 201.51(a) 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).	Adequate	**Recommended revision communicated to OND:** The storage statement on the CC labels should be revised to the uniform storage statement to be consistent with recommendation provided in the PI.
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	

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

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
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 Carton and Container Labeling: *{Inadequate}*

The storage statement in the CC labels should be revised to uniform storage statement for USP controlled room temperature to be consistent with the PI. In addition, the strength on the CC labels should come after the established name.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: Adequate

List of Deficiencies communicated to OND:

Regarding Container and Carton Labels:

1. Revise the storage statement on your container and carton labels to "Store at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C and 30°C (59°F to 86°F). [*See USP Controlled Room Temperature*]" consistent with the recommendation provided for the prescribing information.
2. The strength of the product should be listed after the established name as following:
   "TRIUMEQ PD (abacavir, dolutegravir, and lamivudine) tablets for oral suspension, 60mg/5mg/30mg"

Regarding the Instruction for Use (IFU):

3. Revise the storage statement in your IFU to "Store at 68°F to 77°F (20°C to 25°C); excursion permitted between 59°F to 86°F (15°C and 30°C). [*See USP Controlled Room Temperature*]", to be consistent with the recommendation provided for the prescribing information.

Primary Labeling Assessor Name and Date: 2/25/2022

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

Sheena Hailin Wang

Digitally signed by Sheena Hailin Wang
Date: 2/25/2022 05:47:13PM
GUID: 5203a2110001f7235a14cac1b60d05c4

David Claffey

Digitally signed by David Claffey
Date: 2/28/2022 08:48:21AM
GUID: 508da71e00029e20b201195abff380c2

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/

HAILIN WANG
03/04/2022 01:59:06 PM