CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217660Orig1s000

PRODUCT QUALITY REVIEW(S)

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

DATE: 03-APR-2023

TO: NDA 217660 File

FROM: Craig M. Bertha
Chemistry Reviewer
ONDQA, Division III, Branch VIII

SUBJECT: Labeling Addendum for Integrated Quality Assessment (IQA)

SUMMARY: Labeling negotiations with the applicant were not completed at the time of the due date for the primary reviews (21-MAR-2023). There was one outstanding deficiency regarding the presentation of the drug product proprietary name, established name, dosage form and strength on the carton and wallet. The applicant has adequately addressed the deficiency and has resubmitted the revised carton and container labeling on 31-MAR-2023.

RECOMMENDATION: The NDA 217660 is now ready for approval as per 21 CFR 314.125(b)(6).

ATL: Craig M. Bertha, 03-APR-2023

cc:
OND/OII//DPACC/Kwon
OND/OII/DPACC/JLee
OPQ/ONDP/DNDPII/Branch IV/CBertha
OPQ/ONDP/DNDPII/Branch IV/ZGe
OPQ/OPRO/DRBPMI/RBPMB2/ALalmansingh
OPQ/OPMA/DPMAII/PMB4/HYang
OPQ/OPMA/DPMAII/PMB4/CHu
OPQ/ONDP/BB/DB2/KPaudel
OPQ/ONDP/BB/DB2/TGhosh

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/s/

CRAIG M BERTHA
04/03/2023 11:50:18 AM

Office of Pharmaceutical Quality

New Drug Application (NDA) 217660
Integrated Quality Assessment

Reference ID: 5145054

RECOMMENDATION

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

NDA 217660
Assessment #1

Drug Product Name	Elexacaftor (ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA) oral granules and IVA oral granules
Dosage Form	Oral granules
Strengths	100/50/75 mg and 80/40/60 mg ELX/TEZ/IVA and 75 mg and 59.5 mg IVA
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Vertex Pharmaceuticals Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD 1 (original)	28-OCT-2022	All
SD 6 (amendment)	06-JAN-2023	Manufacturing
SD 8 (amendment)	20-JAN-2023	Drug Product
SD 9 (amendment)	25-JAN-2023	Biopharmaceutics
SD 12 (amendment)	31-JAN-2023	Drug Product
SD 13 (amendment)	07-FEB-2023	Labeling
SD 15 (amendment)	03-MAR-2023	Manufacturing
SD 16 (amendment)	08-MAR-2023	Labeling
SD 17 (amendment)	13-MAR-2023	Manufacturing/Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance[1]	N/A	
Product	Zhengfang Ge	Craig M. Bertha
Manufacturing	Hong Yang	Chengjiu Hu
Microbiology	N/A	
Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	

[1] The information supporting the ELX drug substance was provided by reference to Vertex's approved NDA 212273; Information supporting the IVA (b) (4) was referenced to Vertex' approved NDAs 203188, 207925, and 210491; Information supporting the TEZ (b) (4) was referenced to Vertex's approved NDAs 210491 and 212273. No drug substance reviewer assignment was necessary as a result.

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Reference ID: 5145054

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)			

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

Document	Application Number	Description
IND	132547	ELX/TEZ/IVA oral granules
IND	108105	TEZ/IVA tablets
IND	74633	IVA tablets
NDA	203188	Kalydeco (IVA) tablets
NDA	210491	Symdeko (TEZ/IVA) tablets
NDA	212273	Trikafta (ELX/TEZ/IVA) tablets
NDA	207925	Kalydeco (IVA) granules/oral granules

2. CONSULTS

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

Reference ID: 5145054

NDA Executive Summary

1. Application/Product Information

NDA Number.	217660
Applicant Name	Vertex Pharmaceuticals Inc.
Drug Product Name	ELX/TEZ/IVA oral granules
Dosage Form.	Granule
Proposed Strength(s)	100/50/75 mg and 80/40/60 mg ELX/TEZ/IVA and 75 mg and 59.5 mg IVA
Route of Administration	Oral
Maximum Daily Dose	200 mg ELX, 100 mg TEZ; 300 mg IVA
Rx/OTC Dispensed	Rx
Proposed Indication	"TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation or a mutation that is responsive based on in vitro data."
Drug Product Description	The drug product is a triple fixed dose combination (21 CFR 300.50) of ELX/TEZ/IVA as oral granules with two strength combinations for the morning dose and IVA oral granules with two strengths for the evening dose from Vertex for treatment of cystic fibrosis in patients 2 years and older. The doses should be taken with fat-containing food.

Reference ID: 5145054

Co-packaged product information	The ELX/TEZ/IVA oral granules and the IVA oral granules are co-packaged with 56 count cartons each containing 4 wallets, each wallet containing 7 packets of ELX/TEZ/IVA oral granules and 7 packets of IVA oral granules		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 68ºF - 77ºF (20ºC - 25ºC); excursions permitted to 59ºF - 86ºF (15ºC - 30ºC) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance[1]	N/A	
	Drug Product/ Labeling	Zhengfang Ge	Craig M. Bertha
	Manufacturing	Hong Yang	Chengjiu Hu
	Biopharmaceutics	Kalpana Paudel	Tapash Ghosh
	Microbiology	N/A	
	Other (specify):		
	RBPM	Anika Lalmansingh	
	ATL	Craig M. Bertha	
Consults			

2. Final Overall Recommendation Adequate

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:
All CMC deficiencies have been resolved, thus the application is recommended for approval.[2]

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes (see footnote 1)

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Inadequate**[2]
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

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

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: The original application included a comparability protocol but due to deficiencies, the applicant agreed to withdraw it (see SD 17).

Additional Lifecycle Comments: The applicant has agree to test for degradation products at release for the first ten commercial bulk granule batches and provide the results in the annual report. If degradation products are observed above (b) (4)% w/w in any of the ten batches, Vertex will submit a post-approval supplement to include testing for degradation of the drug substance in the drug product in the specification for the latter at the time of batch release.

Application Technical Lead Name and Date:

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

Reference ID: 5145054

Craig M. Bertha, 21-MAR-2023

Reference ID: 5145054

Final Risk Assessment for Trikafta Oral Granules

DP attribute/ CQA	Factors that may impact the CQA	O[3]	S[4, 4]	D[4]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations
Appearance	• color of input materials • color change during (b) (4)	3	3	2	18	(b) (4)		
Identification	• incorrect (b) (4) material accepted and formulated • incorrect API formulated	1	3	1	3			
Assay	• assay/purity of input ELX, TEZ (b) (4) IVA (b) (4) and excipients • (b) (4) • • variation of packet fill weights	3	3	2	18			

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

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

Final Risk Assessment for Trikafta Oral Granules

						(b) (4)		
Degradation Products	• poor packet seal integrity • high degradant levels in the ELX, TEZ (b) (4) and/or IVA (b) (4) • compatibility of APIs with excipients • degradation of one or more APIs during manufacturing • degradation of APIs on stability	2	3	3	18			
Dissolution	• variability ELX particle size • variability of bulk density of TEZ (b) (4) • variability of bulk density of IVA (b) (4) • (b) (4)	2	3	3	18			
Uniformity of Dosage Units (ivacaftor/lumacaftor have high drug loads)	• variability ELX particle size • variability of bulk density of TEZ (b) (4) • variability of bulk density of IVA (b) (4) • (b) (4) •	2	3	4	24			
Microbial limits	•	1	3	2	6			

Final Risk Assessment for Trikafta Oral Granules

						(b) (4)		
Physical forms	• physical forms of drug substances are potentially altered during processing or with time • change of drug substance crystalline form with food contact	2	3	4	24			
Elemental impurities	• elemental impurities in inpu TEZ (b) (4) IVA (b) (4) excipients • elemental impurities introduced by	2	3	5	30		1x3x5=15	(b) (4)

Final Risk Assessment for Trikafta Oral Granules

	manufacturing equipment/CCS					(b) (4)		(b) (4)
Residual solvents	• residual solvents ELX • residual solvents in TEZ (b) (4) • residual solvents in IVA (b) (4) • residual solvents in excipients	1	3	5	15			
(b) (4)	• Formulation during API manufacture • Formation in drug product as formulated	2	3	3	18			

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRIKAFTA®	**Adequate**
Established name(s)	(elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets) co-packged for oral use (elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules) co-packaged	**Adequate** • See "Evaluation" below regarding using "oral granules" as a dosage form descriptor • (b) (4) has been deleted for the oral granules in SharePoint labeling PI
Route(s) of administration	For the Tablets: co-packaged for oral use	**Adequate**
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: Fixed dose combination containing elexacaftor 50 mg, tezacaftor 25 mg and ivacaftor 37.5 mg co packaged with ivacaftor 75 mg; fixed dose combination containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co packaged with ivacaftor 150 mg. (3) Oral granules: Unit-dose packets of elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg co packaged with unit-dose packets of ivacaftor 75 mg; unit-dose packets of elexacaftor 80 mg, tezacaftor 40 mg and ivacaftor 60 mg co packaged with unit-dose packets of ivacaftor 59.5 mg. (3)	**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	

Evaluation:

The applicant proposed to use "oral granules" as a dosage form descriptor for the co-packaged TRIKAFTA® in this NDA, which is consistent with the IVA oral granules approved for Kalydeco® in NDA 207925. IVA oral granules are also a co-packaged drug product in the current NDA.

A concern was raised by OPQ labeling expert, Mr. J. Abdus-Samad, whether the dosage form should be "oral Granules" or "oral pellets". Per current USP <1151>, "granules" is a dosage form composed of dry aggregates of powder particles that may contain one or more drug substances while "pellets" is a small solid dosage form of uniform, sometimes spherical, shape intended for direct administration. From appearance perspective, "pellets" is a more suitable dosage form descriptor for both co-package drug products, ELX/TEZ/IVA granules and IVA granules. However, since the "oral granules" is already a descriptor for the approved Kalydeco IVA product in NDA 207925, the following comment was conveyed to the applicant dated 1-Mar-2023

- With regard to your labels and labeling, revise the dosage form descriptor from "oral granules" to "oral pellets" based on the updated definitions in the USP general chapter <1151> Pharmaceutical Dosage Forms, where pellets are described as "a small solid dosage form of uniform, sometimes spherical, shape intended for direct administration." There are two options that you may consider: 1) revise the labels/labeling such that all of the dosage forms of NDA 217660 and NDA 207925 use "oral pellets" as opposed to "oral granules" as the dosage form descriptor, or 2) revise only the dosage form descriptor for the elexacaftor, tezacaftor and ivacaftor triple fixed dose combination drug product to "oral pellets" and maintain "oral granules" for the ivacaftor monotherapy drug products for both NDAs.

  We note that the dosage form descriptor for your proposed product will be altered regardless of the aforementioned options you choose to move forward with. Therefore, your proprietary name, Trikafta, which was deemed conditionally acceptable on 2/16/2023 should be resubmitted for review.

  If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

  - Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027

If you have any questions regarding the proprietary name review process, contact Cristina Attinello, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-3986.

We update guidance periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

In a draft response emailed on 7-Mar-2023, Vertex objected to the Agency's request to revise the dosage form descriptor from "oral granules" to "oral pellets" for ELX/TEZ/IVA triple fixed dose combination product for the reasons: 1) it may result in delay of the product for a High Unmet Need Population due to the labeling redesign; 2) it may cause patient confusion for the identical co-packaged products to have different dosage form descriptor; 3) <1151> does not apply since Trikafta drug product is not a monographed product; 4) Kalydeco is an approved drug with "oral granules" descriptor, there is no substantial updates to the definition of granules or pellets since the approval of Kalydeco and the ELX/TEZ/IVA has the identical appearance; 5) <1151> is only informational and not binding; 6) USP disfavors pellets, and ELX/TEZ/IVA granules do not have the characteristics of the pellets defined by USP<1151> such as: physical separation for chemically or physically incompatible materials and for control of release of the drug substance, may be designed with the drug substance dispersed in a matrix or the pellets may be coated with a polymer, manufactured by wet extrusion processes followed by spheronization, by wet or dry coating processes, or by compression; 7) the manufacture of pellets by compression in USP <1151> is largely restricted to the production of material for subcutaneous implantation

An internal meeting was held with ONDP and OPPQ labeling experts, DMEPA (medication errors), and the clinical Division (DPACC). The team discussed the applicant's reasoning for the objection to changing the dosage form descriptors from "oral granules" to "oral pellets" for the ELX/TEZ/IVA, the current USP <1151> definitions for granules and pellets and how the Trikafta dosage forms had some product characteristics that appeared to be consistent with some aspects of each definition in USP <1151>. In the future, the Agency will work with the USP/NF as necessary to attain more clarification of the application of the <1151> definitions to these drug products. If a monograph is

eventually proposed for either of the co-packaged drug products of Trikafta, the dosage form descriptor will likely need to be revisited. However, at the present time, as the 75 mg IVA oral granules monotherapy product that is co-packaged with the ELX/TEZ/IVA oral granules higher strength is well known to patients and has been approved for treatment of CF since March of 2015, the clinical Division and DMEPA had concerns that there would be the potential for patient confusion associated with a change in the dosage form descriptor from "oral granules" to "oral pellets." As a result, it was decided that for the time being, it would be better to maintain the dosage form descriptors as "oral granules" for both co-packaged drug products.

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)	The entire contents of each packet of oral granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and the mixture completely consumed. Food or liquid should be at room temperature or below. Each packet is for single use only. Once mixed, the product has been shown to be stable for one hour, and therefore should be consumed during this period. Some examples of soft food or liquids include pureed fruits or vegetables, yogurt, applesauce, water, milk, or juice. Each dose should be administered just before or just after a fat-containing food.	**Adequate** - In-use stability study was conducted to ensure the granules are stable as stated

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets Oral Granules	**Adequate** - Tablets were approved in NDA 212273
Strength(s) in metric system	for the oral granules 1. elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 75 mg 2. elexacaftor 80 mg, tezacaftor 40 mg, ivacaftor 60 mg co-packaged with ivacaftor 59.5 mg	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Provided as duplicated above	**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 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	

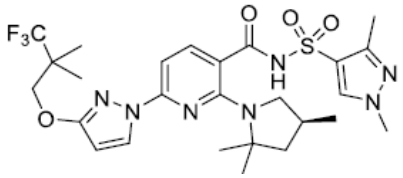
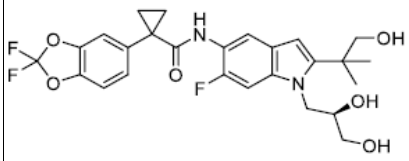
1.2.3 Section 11 (DESCRIPTION)

(b) (4)

Reference ID: 5145054

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

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRIKAFTA is a co-package of elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets or granules and ivacaftor tablets or granules. Both tablets and granules are for oral administration.	**Adequate** - The description noted that both tablets and granules are for oral administration.
Dosage form(s) and route(s) of administration	Tablets and oral granules	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	**Adequate**
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	Not provided for elexacaftor and tezacaftor. Provided for Ivacaftor: Pharmacologically it is a CFTR potentiator	**Adequate** - There are no known pharmacological therapeutic classes for Elexacaftor and tezacaftor per pharmtox reviewer

Chemical name, structural formula, molecular weight	Elexacaftor N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide Molecular formula: C26H34N7O4SF3 Molecular weight: 597.66  Tezacaftor 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide Molecular formula: C26H27N2F3O6 Molecular weight: 520.50  Ivacaftor N-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide Molecular formula: C24H28N2O3 Molecular weight: 392.49	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Elexacaftor is a white solid that is practically insoluble in water (<1 mg/mL). Tezacaftor is a white to off-white solid that is practically insoluble in water (<5 microgram/mL). Ivacaftor is a white to off-white crystalline solid that is practically insoluble in water (<0.05 microgram/mL).	**Adequate**

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)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets, oral granules	**Adequate**
Strength(s) in metric system	provided	**Adequate**
Available units (e.g., bottles of 100 tablets)	56-count packet carton (4 wallets, each containing 7 packets of elexacaftor, tezacaftor, and ivacaftor and 7 packets of ivacaftor)	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white, sweetened, unflavored granules approximately 2 mm in diameter granules	**Adequate** - The description applies to both granule drug products
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
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."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 68°F - 77°F (20°C - 25°C); excursions permitted to 59°F - 86°F (15°C - 30°C) [see USP Controlled Room Temperature].	**Adequate** - A minor change made in the SharePoint labeling: "Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]." Only patient labeling needs to show Fahrenheit ahead of Celsius
Latex: If product does not contain latex and manufacturing	N/A	

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."		
Include information about child-resistant packaging	Not included	

1.2.5 Other Sections of Labeling

N/A

1.2.6 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 Vertex Pharmaceuticals Incorporated 50 Northern Avenue Boston, MA 02210	**Adequate**

2.0 PATIENT LABELING

The following CMC Information for the oral granules in the Patient Labeling is adequate.

(b) (4)

3.0 CARTON AND CONTAINER LABELING

Labels for carton, wallet and packet provided below are for the strengths of TRIKAFTA (elexacaftor/tezacaftor/ivacaftor and ivacaftor) 100 mg/50 mg/75 mg and 75 mg oral granules, Labels for the strengths at 80 mg/40 mg/60 mg and 59.5 mg oral granules are similar except the difference in strength

Carton Label

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Reference ID: 5145054

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	On carton and wallet: Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) 100 mg/50 mg/75 mg and 75 mg oral granules on ELX/TEZ/IVA packet: elexacaftor/tezacaftor/ivacaftor oral granules 100 mg ·50 mg · 75 mg On IVA packet ivacaftor oral granules 75 mg	**Not Adequate** - As per the PQL team in OPPQ (electronic mail from Jibril Abdus-Samad dated 3/13/2023), the dosage from should appear with each of the established names for the co-packaged drug product. Change the drug product name, established name and dosage form on the carton and wallet to the following format for each strength combination: Trikafta (elexacaftor, tezacaftor and ivacaftor) oral granules 100 mg/50 mg/75 mg; co-packaged with (ivacaftor) oral granules 75 mg
Dosage strength	100 mg/50 mg/75 mg and 75 mg or 80 mg/40 mg/60 mg and 59.5 mg	**Adequate**
Route of administration	Oral granules	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	On Wallet: 14 packets 7 packets of elexacaftor, tezacaftor and ivacaftor and 7 packets of ivacaftor. On Carton: 56 packets Carton contains: 4 individual wallets with 14 packets per wallet	**Adequate**
"Rx only" displayed on the principal display	Provided on carton, wallet and packet	**Adequate**
NDC number	Provided on carton, wallet and packet	**Adequate**
Lot number and expiration date	Provided on carton and packet, but not wallet	**Adequate** - See Assessment below

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	On carton and wallet: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature	**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 on carton and packet, but not wallet	**Adequate** - See Assessment below
Name of manufacturer/distributor	On carton and wallet: Manufactured for: Vertex Pharmaceuticals Incorporated Boston, MA 02210	**Adequate**
Medication Guide (if applicable)	Provided on the back of wallet label as duplicated above	**Adequate**
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.	Morning and evening packets indicated on the wallet	**Adequate**
And others, if space is available	N/A	

Assessment of Carton, Wallet and Container Labeling: *Not Adequate*

The following request was conveyed to the applicant on 1-Mar-2023:

1. Include lot number and expiration date on the wallet label
2. Include bar code on the wallet label

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

In a response to the Agency's request dated 8-Mar-2023, the applicant accepted the request 3 and provided updated mock-up.

For requests 1 and 2, the applicant explained that Product identifiers, as defined by the FD&C act include NDC, serial number, lot number, and expiration date, in both human and machine readable (bar code) format, are required to "be affixed or imprinted on the smallest individual saleable unit of product for distribution …". Additionally, per CFR §201.17, the expiration date is not required on the wallet label because when an expiration date of a drug is required, e.g., expiration dating of drug products required by § 211.137 of this chapter, it shall appear on the immediate container and the outer package, if any, unless it is easily legible through such outer package. However, when single-dose containers are packed in individual cartons, the expiration date may properly appear on the individual carton instead of the immediate product container. Per §201.25(c)(2), the bar code should appear on the label in accordance with section 201(k). Section 201(k) states: The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper. In the case of Trikafta, the smallest individual saleable unit is the carton, and the lot number, expiration date and bar code are included on both the sachet ("immediate container") and carton ("outer package") and therefore meets the requirements of the act. Inclusion of this information (on wallet) is not required by regulation, nor does it provide additional clarity or information to the patient. The applicant's response is consistent with the recommendation outlined in our guidance entitled Product Identifiers Under the Drug Supply Chain Security Act; Questions and Answers (2018) for the placement of the product identifiers and therefore is acceptable.

The dosage from should appear with each of the established name for the co-packaged drug product, the applicant should be requested to change the drug product name, established name and dosage form on the carton and wallet to the following format for each strength combination:

Trikafta
(elexacaftor, tezacaftor and ivacaftor) oral granules 100 mg/50 mg/75 mg;
co-packaged with
(ivacaftor) oral granules 75 mg

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

Minor editorial changes have been made in the PI in SharePoint.

The following request for the carton and container labels should be conveyed to the applicant:

- Change the drug product proprietary name, established name, dosage form and strength on the carton and wallet to the following:

Trikafta
(elexacaftor, tezacaftor and ivacaftor) oral granules 100 mg/50 mg/75 mg;
co-packaged with
(ivacaftor) oral granules 75 mg

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

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

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

Craig Bertha, Ph. D.
Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 3/14/2023 01:58:43PM
GUID: 508da7210002a030e76df4f60ccd142a

Craig Bertha

Digitally signed by Craig Bertha
Date: 3/15/2023 06:00:05AM
GUID: 50841a65000098a9383c817879a6a84d

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BIOPHARMACEUTICS

NDA: 217660

Drug Product Name / Strength: Trikafta (elexacaftor/tezacaftor/ivacaftor) Granules (100/50/75 & 80/40/60mg); IVA 59.5 mg Granules

Indication: Cystic fibrosis

Route of Administration: Oral

Applicant Name: Vertex Pharmaceuticals Incorporated

Product Background:
TRIKAFTA® tablets, which are a fixed-dose combination (FDC) formulation of the active ingredients elexacaftor (ELX, VX-445), tezacaftor (TEZ, VX-661), and ivacaftor (IVA, VX-770) for oral administration, was first approved in the US on October 21, 2019 (NDA 212273; ELX 100 mg/ TEZ 50 mg/ IVA 75 mg) for the treatment of CF in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. On 08 June 2021, an indication extension to include patients aged 6 through 11 years old (sNDA 212273/S-004) and a new tablet strength of ELX 50 mg/ TEZ 25 mg/ IVA 37.5 mg tablets was approved.

In this NDA (217660), the Applicant submitted a new dosage form of the ELX/TEZ/IVA FDC granules in sachets for the treatment of CF in patients 2 through 5 years of age that have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data. The two proposed dosing regimens for TRIKAFTA® granules are (1) ELX 100 mg / TEZ 50 mg / IVA 75 mg FDC granules and IVA 75 mg granules; and (2) ELX 80 mg/ TEZ 40 mg/ IVA 60 mg FDC granules and IVA 59.5 mg granules with a following proposed commercial dosing regimens for patients 2 through <6 years of age:
• Patients weighing ≥14 kg: a morning dose of one sachet containing ELX 100 mg/ TEZ 50 mg/ IVA 75 mg granules daily, and an evening dose of one sachet of IVA 75 mg granules approximately 12 hours apart
• Patients weighing <14 kg: a morning dose of one sachet containing ELX 80 mg/ TEZ 40 mg/ IVA 60 mg once daily, and an evening dose of one sachet of IVA 59.5 mg granules approximately 12 hours apart

Quality information for the ELX/TEZ/IVA granules drug product and IVA 59.5 mg granules strength is included in this submission. Quality information regarding the IVA 75 mg granules strength was previously approved as part of the KALYDECO® granules marketing application (NDA 207925) and is not resubmitted in NDA 217660.

The applicant noted that 59.5 mg ivacaftor granules are for an evening dose intended to be prescribed only in combination with elexacaftor/tezacaftor/ivacaftor 80/40/60 mg fixed-dose combination granules. They are not intended to be commercialized as a Kalydeco monotherapy and will not be submitted to the Kalydeco granules NDA (NDA 207925).

Review Recommendation: **ADEQUATE**

Review Summary:
Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method and acceptance criteria for elexacaftor, tezacaftor and ivacaftor in the FDC granules, and bridging of formulations.

In Vitro Dissolution Method and Acceptance Criterion: ADEQUATE
The following dissolution methods and acceptance criteria for the release of elexacaftor, tezacaftor and, ivacaftor from the FDC granules of both formulation strengths 100/50/75 mg and 80/40/60 mg are deemed acceptable for quality control purposes:

Component	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criterion
Elexacaftor	II (Paddle)	65	1.8% (v/v) Tween 20 in 50 mM sodium phosphate, pH 6.8/37°C ± 0.5°C	900	Q = (b) (4) in 30 minutes
Tezacaftor	II (Paddle)	65	0.1% (w/v) SLS in 0.1N HCl	900	Q = (b) (4)% in 15 minutes
Ivacaftor	II (Paddle)	65	0.4% (w/v) SLS in 50 mM sodium Phosphate buffer, pH 6.8	900	Q = (b) (4) in 20 minutes

Formulation development and bridging of formulations: ADEQUATE from Biopharm perspective
This submission is supported by the results of a phase 1 relative bioavailability of ELX/TEZ/IVA FDCs study (Study 012) and a Phase 1 taste assessment of ELX/TEZ/IVA FDC granules study (Study 013). The main clinical study supporting this submission is Study 111: a Phase 3, 2-part (Part A and B) study. Study 111 was designed to assess PK exposures (Part A) and safety and efficacy (Part B) of ELX/TEZ/IVA. Phase 3 pivotal studies were dosed with the ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg granules for the morning dose. The pivotal studies also dosed 75 mg IVA granules and 59.5 mg IVA granules for the evening doses. The final commercial packaging configuration is sachets, which was used in Study 111 Part B. Prior to sachets, capsules were used as the primary packaging configuration in Studies 111 Part A, 012, and 013.

The Phase 3 composition is also the intended commercial composition. The final commercial formulation strengths are ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg. The dissolution profiles for the Phase 3 clinical/stability batches of all strengths showed rapid release of all three components (more than (b) (4)% dissolution within 30 minutes) from the FDC drug product.

Biowaiver Request: Not Applicable
Both commercial strengths of FDC granules (ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg) were used in Pivotal Phase 3 study (Study 111) according to the body weight of CF subjects 2 through 5 years of age. Dissolution profiles for both strengths are similar.

List of Submissions being reviewed:

Application 217600 - Sequence 0001 Original
Application 217600 - Sequence 0009 (Response to IR)

Highlight Key Outstanding Issues from Last Cycle: None.
Concise Description Outstanding Issues Remaining: None.

Conclusions and recommendation:
From Biopharmaceutics perspective, NDA 217660 for elexacaftor, tezacaftor, and ivacaftor granules of formulation strengths 100/50/75 mg and 80/40/60 mg and ivacaftor granules 59.5 mg are recommended for APPROVAL.

BCS Designation
Reviewer's Assessment: Adequate
The Applicant has not claimed or requested any BCS classification for their drug product. However, following information has been provided in M.2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods). The information was previously submitted for Trikafta FDC Tablet (NDA 212273).

ELX could not be classified definitively by the BCS. ELX drug substance is practically insoluble (<0.1 mg/mL: practically insoluble) in pH buffer solutions of pH 1.0 to pH 8.0. A 100-mg strength tablet requires >1000 mL of aqueous media to dissolve; therefore, ELX is classified as low solubility according to BCS criteria. ELX has high permeability as assessed via the colorectal adenocarcinoma (Caco-2) cell system. In addition, absolute BA of ELX was determined in humans and is approximately 80% (summarized in initial ELX/TEZ/IVA Marketing Application Module 2.7.1/Section 3.3.1), suggesting that permeability is not absorption-limiting (Refer to the initial ELX/TEZ/IVA Marketing Application for details).

TEZ is considered as a BCS Class 2 compound (low solubility/high permeability) (summarized in Symdeko, Symkevi Marketing Authorization/Module 2.7.1/Section 3.6).

IVA could not be definitively classified by the BCS (summarized in Kalydeco Marketing Authorization/ Module 2.7.1/Section 1.5). It has low solubility, suggesting that it is either BCS Class 2 (low solubility/high permeability) or Class 4 (low solubility/low permeability).

Solubility:
The solubility of all three components in different media is provided below.

Elexacaftor

Table 1: Elexacaftor Solubility in Aqueous Buffers, 37°C[a]

Buffer/pH	Elexacaftor Solubility (mg/mL)
0.1 N HCl pH 1.0	None Detected
50 mM Sodium Acetate pH 4.5	None Detected
50 mM Sodium Phosphate pH 6.8	None Detected

[a] Solubility was measured in the presence of ivacaftor (b) (4) and tezacaftor (b) (4) Solubility was determined at 24 hours

Reference ID: 5145054

Table 2: Elexacaftor Solubility in Surfactant / Buffer Combinations, 37°C[a]

Surfactant / Surfactant Type	Surfactant Level (% w/v)[b]	Buffer	Solubility (mg/mL)[c]
CTAB / cationic	0.8	0.1 N HCl, pH 1.0	0.05
	0.5	0.1 N HCl, pH 1.0	0.12
	0.3	0.1 N HCl, pH 1.0	0.04
	0.8	50 mM sodium acetate, pH 4.5	0.76
	0.5	50 mM sodium acetate, pH 4.5	0.77
	0.3	50 mM sodium acetate, pH 4.5	0.38
	0.8	50 mM sodium phosphate, pH 6.8	1.06
	0.5	50 mM sodium phosphate, pH 6.8	1.18
	0.3	50 mM sodium phosphate, pH 6.8	1.93
SLS / anionic	1.7	0.1 N HCl, pH 1.0	0.40
	1.6	0.1 N HCl, pH 1.0	0.36
	1.5	0.1 N HCl, pH 1.0	0.42
	2.0	50 mM sodium acetate, pH 4.5	0.16
	1.0	50 mM sodium acetate, pH 4.5	0.08
	0.5	50 mM sodium acetate, pH 4.5	0.05
	2.0	50 mM sodium phosphate, pH 6.8	0.25
	1.0	50 mM sodium phosphate, pH 6.8	0.12
	0.5	50 mM sodium phosphate, pH 6.8	0.08
	0.1	50 mM sodium phosphate, pH 6.8	0.05
Tween 80 / non-ionic[b]	2.0	0.1 N HCl, pH 1.0	0.07
	1.0	0.1 N HCl, pH 1.0	0.04
	2.0	50 mM sodium acetate, pH 4.5	0.09
	1.0	50 mM sodium acetate, pH 4.5	0.04
	2.0	50 mM sodium phosphate, pH 6.8	0.44
	1.0	50 mM sodium phosphate, pH 6.8	0.27
Tween 20 / non-ionic[b]	2.5	50 mM sodium phosphate, pH 6.8	1.16
	2.0	50 mM sodium phosphate, pH 6.8	0.83
	1.8	50 mM sodium phosphate, pH 6.8	0.77
	1.5	50 mM sodium phosphate, pH 6.8	0.62
	1.0	50 mM sodium phosphate, pH 6.8	0.45
Brij 35 / non-ionic	2.0	50 mM sodium phosphate, pH 5.5	0.21
	1.5	50 mM sodium phosphate, pH 5.5	0.15
	1.0	50 mM sodium phosphate, pH 5.5	0.08
	0.5	50 mM sodium phosphate, pH 5.5	0.04
Triton X-100 / non-ionic[b]	1.0	0.1 N HCl, pH 1.0	<DL[d]
	0.5	0.1 N HCl, pH 1.0	0.01

[a] Solubility was measured in the presence of ivacaftor (b) (4) and tezacaftor (b) (4) Solubility was determined at 24 hours.
[b] Surfactant level unit for Tween 80, Tween 20, and Triton X-100 is % (v/v)
[c] Sink conditions for elexacaftor at the ELX/TEZ/IVA 100/50/75 mg dose level is 0.33 mg/mL
[d] DL = Detection Limit

Tezacaftor

Table 3: Tezacaftor (b) (4) Solubility in Aqueous Buffers, 37°C[a]

Buffer/pH	Tezacaftor Solubility (mg/mL)
0.1 N HCl pH 1.0	0.004
50 mM Sodium Acetate pH 4.5	0.003
50 mM Sodium Phosphate pH 6.8	0.005

[a] Solubility was measured in the presence of elexacaftor DS and ivacaftor (b) (4) Solubility was determined at 24 hours.

Table 4: Tezacaftor (b) (4) Solubility in Surfactant / Buffer Combinations, 37°C[a]

Surfactant / Surfactant Type	Surfactant Level (% w/v)[b]	Buffer	Solubility (mg/mL)[c]
CTAB / cationic	0.8	0.1 N HCl, pH 1.0	0.41
	0.5	0.1 N HCl, pH 1.0	0.52
	0.3	0.1 N HCl, pH 1.0	0.48
	0.8	50 mM sodium acetate, pH 4.5	0.54
	0.5	50 mM sodium acetate, pH 4.5	0.52
	0.3	50 mM sodium acetate, pH 4.5	0.54
	0.8	50 mM sodium phosphate, pH 6.8	0.58
	0.5	50 mM sodium phosphate, pH 6.8	0.59
	0.3	50 mM sodium phosphate, pH 6.8	0.75
Surfactant / Surfactant Type	**Surfactant Level (% w/v)[b]**	**Buffer**	**Solubility (mg/mL)[c]**
SLS / anionic	2.0	0.1 N HCl, pH 1.0	0.53
	1.0	0.1 N HCl, pH 1.0	0.53
	0.5	0.1 N HCl, pH 1.0	0.45
	2.0	50 mM sodium acetate, pH 4.5	0.53
	1.0	50 mM sodium acetate, pH 4.5	0.53
	0.5	50 mM sodium acetate, pH 4.5	0.45
	2.0	50 mM sodium phosphate, pH 6.8	0.56
	1.0	50 mM sodium phosphate, pH 6.8	0.53
	0.5	50 mM sodium phosphate, pH 6.8	0.49
Tween 80 / non-ionic[b]	2.0	0.1 N HCl, pH 1.0	0.49
	1.0	0.1 N HCl, pH 1.0	0.49
	2.0	50 mM sodium acetate, pH 4.5	0.49
	1.0	50 mM sodium acetate, pH 4.5	0.41
	2.0	50 mM sodium phosphate, pH 6.8	0.56
	1.0	50 mM sodium phosphate, pH 6.8	0.51
Brij 35 / non-ionic	2.0	50 mM sodium phosphate, pH 5.5	2.25
	1.5	50 mM sodium phosphate, pH 5.5	2.15
	1.0	50 mM sodium phosphate, pH 5.5	1.32
	0.5	50 mM sodium phosphate, pH 5.5	0.46
Triton X-100 / non-ionic[b]	1.0	0.1 N HCl, pH 1.0	0.03
	0.5	0.1 N HCl, pH 1.0	0.06

[a] Solubility was measured in the presence of elexacaftor DS and ivacaftor (b) (4) Solubility was determined at 24 hours.
[b] Surfactant level unit for Tween 80 and Triton X-100 is % (v/v).
[c] Sink conditions for tezacaftor at the ELX/TEZ/IVA 100/50/75 mg dose level is 0.17 mg/mL

Ivacaftor

Table 5: Ivacaftor (b) (4) Solubility in Aqueous Buffers, 37°C[a]

Buffer/pH	Ivacaftor Solubility (mg/mL)
0.1 N HCl pH 1.0	None Detected
50 mM Sodium Acetate pH 4.5	None Detected
50 mM Sodium Phosphate pH 6.8	None Detected

[a] Solubility was measured in the presence of elexacaftor DS and tezacaftor (b) (4) Solubility was determined at 24 hours.

Table 6: Ivacaftor (b) (4) Solubility in Surfactant / Buffer Combinations, 37°C[a]

Surfactant / Surfactant Type	Surfactant Level (% w/v)[b]	Buffer	Solubility (mg/mL)[c]
CTAB / cationic	0.8	0.1 N HCl, pH 1.0	0.53
	0.5	0.1 N HCl, pH 1.0	0.64
	0.3	0.1 N HCl, pH 1.0	0.53
	0.8	50 mM sodium acetate, pH 4.5	0.75
	0.5	50 mM sodium acetate, pH 4.5	0.79
	0.3	50 mM sodium acetate, pH 4.5	0.74
	1.0	50 mM sodium phosphate, pH 6.8	2.23
	0.5	50 mM sodium phosphate, pH 6.8	0.85
SLS / anionic	1.0	0.1 N HCl, pH 1.0	0.21
	0.5	0.1 N HCl, pH 1.0	0.24
	2.0	50 mM sodium acetate, pH 4.5	0.63
	1.0	50 mM sodium acetate, pH 4.5	0.16
	0.5	50 mM sodium acetate, pH 4.5	0.33
	2.0	50 mM sodium phosphate, pH 6.8	0.54
	0.5	50 mM sodium phosphate, pH 6.8	0.39
	0.1	50 mM sodium phosphate, pH 6.8	0.13
Tween 80 / non-ionic[b]	2.0	0.1 N HCl, pH 1.0	0.72
	1.0	0.1 N HCl, pH 1.0	0.30
	2.0	50 mM sodium acetate, pH 4.5	0.74
	1.0	50 mM sodium acetate, pH 4.5	0.27
	2.0	50 mM sodium phosphate, pH 6.8	0.80
	1.0	50 mM sodium phosphate, pH 6.8	0.32
Brij 35 / non-ionic	2.0	50 mM sodium phosphate, pH 5.5	1.02
	1.5	50 mM sodium phosphate, pH 5.5	0.76
	1.0	50 mM sodium phosphate, pH 5.5	0.53
	0.5	50 mM sodium phosphate, pH 5.5	0.30
Triton X-100 / non-ionic[b]	1.0	0.1 N HCl, pH 1.0	0.04
	0.5	0.1 N HCl, pH 1.0	0.07

[a] Solubility was measured in the presence of elexacaftor DS and tezacaftor (b) (4) Solubility was determined at 24 hours.
[b] Surfactant level unit for Tween 80 and Triton X-100 is % (v/v)
[c] Sink conditions for ivacaftor at the ELX/TEZ/IVA 100/50/75 mg dose level is 0.25 mg/mL

Dissolution: Please see below.

Composition of proposed drug product:

ELX/TEZ/IVA granules are a fixed-dose combination formulation for oral administration. Elexacaftor is provided as a (b) (4) Tezacaftor and Ivacaftor are provided as individual (b) (4) The ELX/TEZ/IVA granules are (b) (4) granules with a nominal diameter of 2 mm and an (b) (4) The granules are (b) (4) of 100 mg elexacaftor/50 mg tezacaftor/75 mg ivacaftor or 80 mg elexacaftor/40 mg tezacaftor/60 mg ivacaftor. An additional strength of 40 mg elexacaftor/20 mg tezacaftor/30 mg ivacaftor was developed to support the bracketing stability approach described in Section 3.2.P.8.1.

The quantitative composition of the FDC drug product is provided below.

Table 7: Composition of VX-445/Tezacaftor/Ivacaftor Fixed Dose Combination Granules

APPEARS THIS WAY ON ORIGINAL

Component	Quality Standard	Component Function	Amount per unit dose (mg) ELX/TEZ/IVA (mg/mg/mg) 100/50/75	80/40/60	Granule Content (% w/w)
Elexacaftor drug substance	Internal standard	Active ingredient	100.0	80.0	(b) (4)
Tezacaftor (b) (4)	Internal standard	Active ingredient	(b) (4)		
Ivacaftor (b) (4)	Internal standard	Active ingredient			
Lactose monohydrate	USP/NF	(b) (4)			
Mannitol	USP/NF				
Croscarmellose sodium	USP/NF				
Sucralose	USP/NF				
Magnesium stearate	USP/NF				
Colloidal silicon dioxide	USP/NF				
Total	--	--			
Granules per unit dose	--	--			

[a] The 40/20/30 mg strength was used for bracketing stability only.

In vitro dissolution method and acceptance criterion: Adequate

Three independent in vitro dissolution methods were developed for testing the ELX/TEZ/IVA FDC granules, one for each active ingredient. The Applicant submitted dissolution method development report including discriminating ability data. The details of the dissolution method development for each component in the FDC granule is provided in the document \\CDSESUB1\EVSPROD\nda217660\0001\m3\32-body-data\32p-drug-prod\iva-granules-all\32p2-pharm-dev\p22-formulation-dev.pdf

The solubility results of ELX, TEZ, and IVA drug substance in aqueous solutions of varying pH showed no detectable level of ELX and IVA and low levels of TEZ as shown in Tables 1, 3 and 5. Therefore, the applicant explored use of a surfactant to achieve sink conditions for all components. The Applicant's selection of the surfactant, and surfactant concentration were justified adequately. Similarly, the selection of dissolution apparatus, paddle speed, pH, and buffer are acceptable. The provided data show that all dissolution methods are sensitive to changes in material attributes and process parameters. However, the proposed acceptance criteria are not able to discriminate them. The acceptance criteria are set based on the data from Pivotal clinical batches which are rapidly dissolving (more than (b) (4)% dissolution within 30 minutes). Hence, the risk is low from Biopharmaceutics perspective. Overall, the dissolution method is deemed acceptable for the release of elexacaftor, tezacaftor, and ivacaftor from ELX/TEZ/IVA FDC granules for quality control purposes.
The final dissolution method conditions are tabulated in the executive summary of this review and also provided in the link below:
\\CDSESUB1\EVSPROD\nda217660\0001\m3\32-body-data\32p-drug-prod\iva-granules-all\32p5-contr-drug-prod\32p52-analyt-proc\ap-dissolution.pdf

The analytical method for the dissolution was fully validated by performing the specificity, linearity, precision, accuracy, range, robustness, and solution stability. This information will be reviewed by Drug Product reviewer. Please refer to the DP review in Panorama for additional details.
\\CDSESUB1\EVSPROD\nda217660\0001\m3\32-body-data\32p-drug-prod\iva-granules-all\32p5-contr-drug-prod\32p53-val-analyt-proc\vap-dissolution.pdf

The Applicant provided dissolution data for the Phase 3 and/or Primary Stability batches for the three strengths generated using the currently proposed QC method. Profiles are shown in figures below.

Figure 1: Elexacaftor Dissolution Results for Phase 3 and/or Primary Stability Batches of ELX/TEZ/IVA 100/50/75 mg, 80/40/60 mg and 40/20/30 mg Granules in 1.8% (v/v) Tween 20 in 50 mM sodium phosphate pH 6.8, 65 rpm

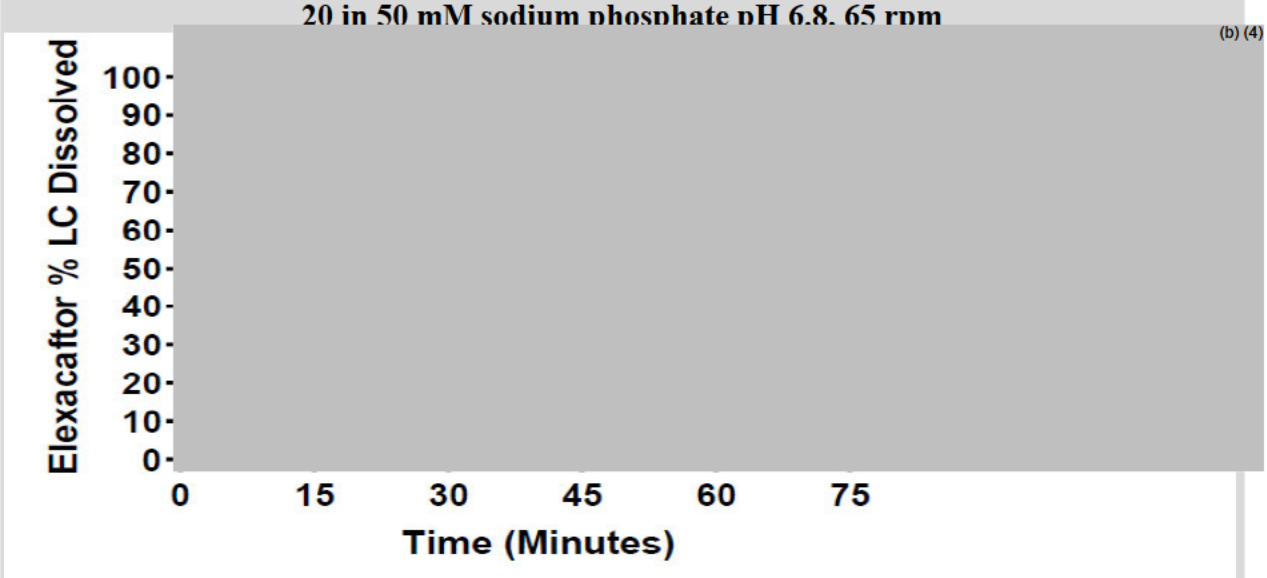


Figure 2: Tezacaftor Dissolution Results for Phase 3 and/or Primary Stability Batches of ELX/TEZ/IVA 100/50/75 mg, 80/40/60 mg and 40/20/30 mg Granules in 0.1% (w/v) SLS in 0.1 N HCl, 65 rpm

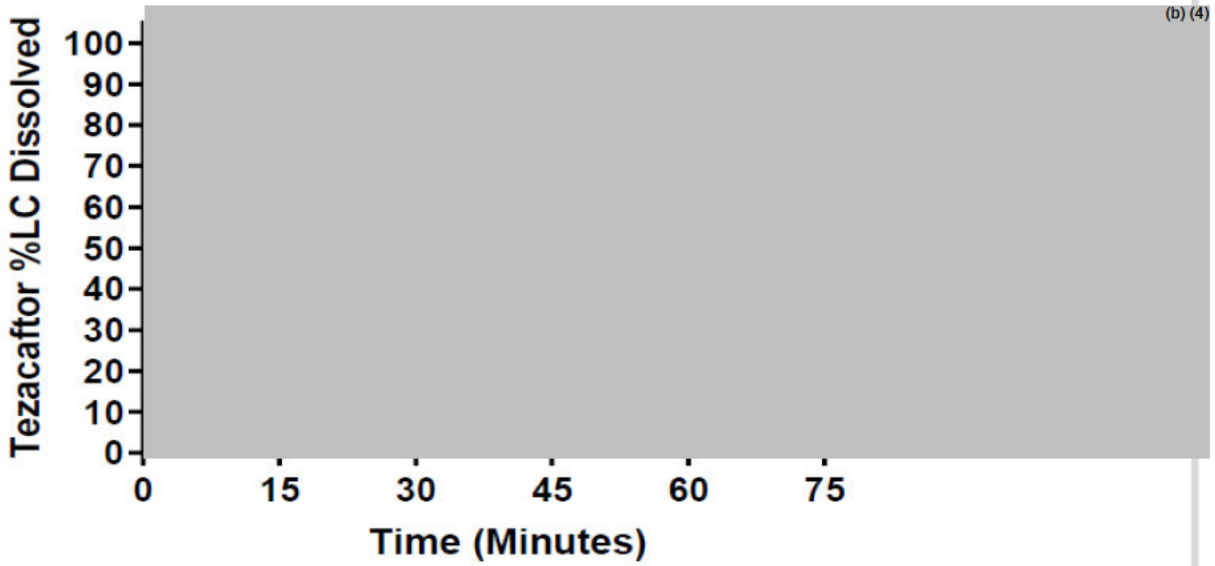
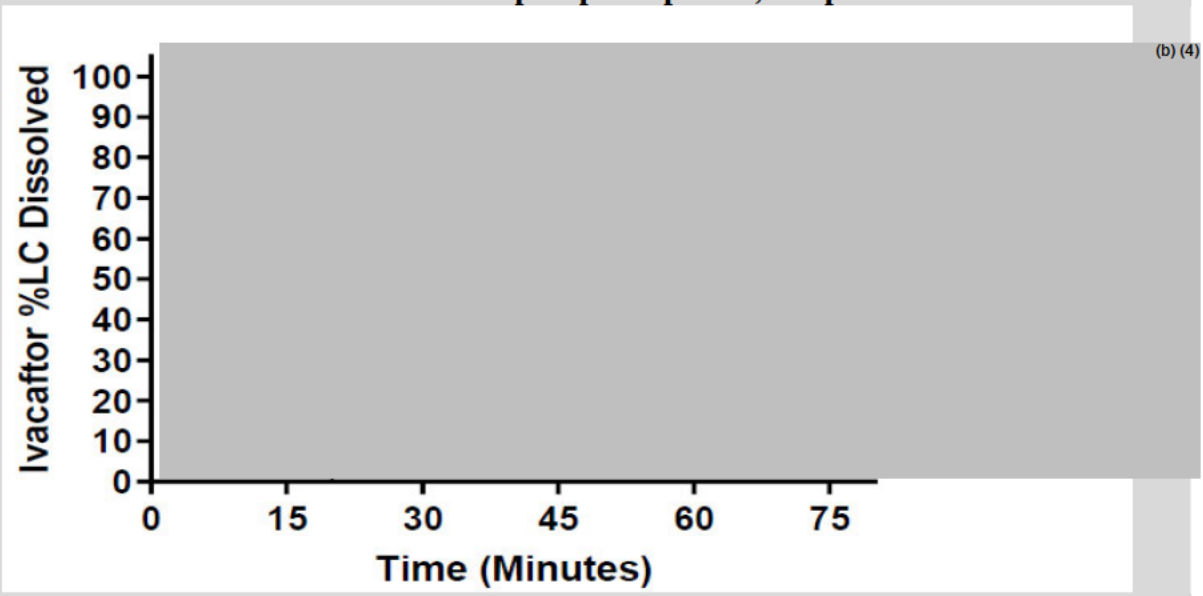


Figure 3: Ivacaftor Dissolution Results for Phase 3 and/or Primary Stability Batches of ELX/TEZ/IVA 100/50/75 mg, 80/40/60 mg, and 40/20/30 mg Granules in 0.4% (w/v) SLS in 50 mM sodium phosphate pH 6.8, 65 rpm



Individual data for these profiles could not be located in the original submission. In addition, dissolution data for the Phase 3 clinical batches could not be identified. Hence, the applicant was requested to provide this information. In response to an IR (Refer to IR1 in the Appendix), the Applicant provided individual profile data for clinical/stability batches of all strengths. The details are provided in the links below.
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\\CDSESUB1\EVSPROD\nda217660\0009\m3\32-body-data\32r-reg-info\elx-tez-iva-granules-dissolution-data-resp.xlsx

The Applicant's proposed acceptance criterion for ELX, TEZ, and IVA are deemed acceptable based on the dissolution data provided.

Dissolution method and acceptance criterion for 75 mg ivacaftor granules (for Evening dose) has been approved previously (please refer to review by Dr. Kareen Riviere dated 01/07/2015 for NDA 207925). The dissolution method and acceptance criterion for the proposed 59.5 mg IVA granules are same as those for commercial 25 mg, 50 mg, and 75 mg granules. The 59.5 mg ivacaftor granules differ from the approved Kalydeco granules strengths of 25, 50, and 75 mg, only with respect to the amount of granules that are filled into the sachets (primary packaging). The method is also the same as proposed for the release of IVA from FDC granules. Stability and manufacturing conclusions for the 59.5 mg ivacaftor granules are bracketed by the approved Kalydeco granules strengths. Batch analyses results for IVA granules 59.5 mg (packet) show that batches met the proposed dissolution acceptance criteria for IVA.

Formulation development and bridging: Adequate

This submission is supported by the results of a phase 1 relative bioavailability of ELX/TEZ/IVA FDCs study (Study 012) and a Phase 1 taste assessment of ELX/TEZ/IVA FDC granules study (Study 013). The main clinical study supporting this submission is Study 111: a Phase 3, 2-part (Part A and B) study. Study 111 was designed to assess PK exposures (Part A) and safety and efficacy (Part B) of ELX/TEZ/IVA. Phase 3 pivotal studies were dosed with the ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg granules for the morning dose. The pivotal studies also dosed 75 mg IVA granules and 59.5 mg IVA granules for the evening doses. The final commercial packaging configuration is sachets, which was used in Study 111 Part B. Prior to sachets, capsules were used as the primary packaging configuration in Studies 111 Part A, 012, and 013. A summary of the formulation development of ELX/TEZ/IVA granules drug product is described below.

Table 8: Formulations of Granules Used in Clinical Studies

Formulation Description	Clinical Study Number (abbreviated)	
	Phase 1	Phase 3
ELX/TEZ/IVA 100/50/75 mg granules in capsule[a]	012 013	111 (Part A)
ELX/TEZ/IVA 100/50/75 mg granules in sachet	n/a	111 (Part B)
ELX/TEZ/IVA 80/40/60 mg granules in sachet	n/a	111 (Part B)
IVA 75 mg granules in sachet[b]	n/a	111 (Part A and B)
IVA 59.5 mg granules in sachet	n/a	111 (Part B)

[a] Capsules used as primary packaging. Empty capsules were discarded after contents were emptied and mixed with small amount of liquid or soft food for oral administration.
[b] Same composition as commercial IVA granules (Kalydeco).

The Phase 3 composition is also the intended commercial composition (Table 7). The final commercial formulation strengths are ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg. The dissolution profiles for the Phase 3 clinical/stability batches of all strengths showed rapid release of all three components (more than (b) (4)% dissolution within 30 minutes) from the FDC drug product.

Biowaiver Request: Not Applicable

The Applicant has not requested any biowaiver. Both commercial strengths of FDC granules (ELX/TEZ/IVA 100/50/75 mg and 80/40/60 mg) were used in Pivotal Phase 3 study (Study 111) according to the body weight of CF subjects 2 through 5 years of age. Dissolution profiles for both strengths are similar.

Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.
***Secondary Reviewer Name*:** Tapash Ghosh, Ph.D.

Appendix

List of Deficiencies communicated to the Applicant during the current review cycle

Information Request 1 (IR 1)

1. We could not locate individual data for dissolution profiles provided in Figures 1, 7 and 16 in M.3.2.P.2.2. Please provide complete dissolution profile data (individual, range, mean, %CV, mean graphical profiles using the proposed dissolution conditions for all the pivotal Phase 3 clinical and primary stability batches of all strengths in a tabulated form. Provide all data in *Microsoft Excel ".xls or .xlsx" format*. Also provide the details on manufacturing date, site, size and the dissolution test date. Identify clinical (including study number) and stability batches.

Kalpana Paudel

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Date: 3/06/2023 12:18:40PM
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Tapash Ghosh

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Date: 3/08/2023 09:51:46AM
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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/

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