CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207925Orig1s000

CHEMISTRY REVIEW(S)

Chemistry Review Cover Sheet

NDA 207925
Kalydeco (ivacaftor) Granules

Edwin Jao, Ph. D.
OPF Division III/Branch VII

Table of Contents

Review Data Sheet

1. NDA 207925

2. REVIEW #:1

3. REVIEW DATE: January 25, 2015

4. REVIEWER: Edwin Jao, Ph. D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Date	Comment
Original	9/17/2014	

7. NAME & ADDRESS OF APPLICANT:

Vertex Pharmaceuticals
Incorporated
130 Waverly Street
Cambridge, MA 02139

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Kalydeco
b) Non-Proprietary Name (USAN): Ivacaftor
c) Code Name/# VX-770
d) Chem. Type/Submission Priority
   - Chem. Type: 1
   - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: No pharmacologic class has been agreed upon

11. DOSAGE FORM: oral granules

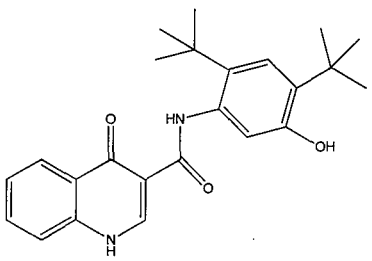
12. STRENGTH/POTENCY: 50 and 75 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular formula: $C_{24}H_{28}N_2O_3$
Molecular weight: 392.49 grams per mole

17. RELATED/SUPPORTING DOCUMENTS:
NDA 203188: for the drug substance Spray Dried Dispersion (SDD) Ivacaftor

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED
(b) (4)	IV		(b) (4)	Adequate information provided in NDA, the DMF Not reviewed	

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74633	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	pending		
Methods Validation	NA		
EA	N/A		
Microbiology	N/A		

The Chemistry Review for NDA 207925

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a CMC perspective pending on the final acceptable recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance (b) (4) *Ivacaftor is* (b) (4) *used in the manufacturing of kalydeco (Ivacaftor) 150 mg tablets (NDA 203188, approved on 1/31/2012, also owned by Vertex). All drug substance CMC information is referred to NDA 203188 accordingly.*

2. Drug Product

The drug product Ivacaftor granules is an immediate release dosage form for oral administration intended for the treatment of cystic fibrosis (CF) in patients age 2 years and older and with certain mutations. The ivacaftor granule has a (b) (4) *target weight of 6.87 mg. Each granule contains a target of* (b) (4) *of ivacaftor. The excipients include colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate, all of compendial grade. The composition of the granules is similar to that of the approved 150 mg tablets but without coating, and with mannitol, sucralose* (b) (4)*. Two strengths of the drug product will be marketed, i.e., 50 mg and 75 mg per packet. Both strengths are filled with the same granules but with different fill weight.*

(b) (4)

The proposed dosage form is granules, which is concurred by ONDP at the precedence meeting.

The drug product is manufactured by (b) (4) *. The manufacturing process includes* (b) (4) *the unit dose, 50 mg or 75 mg. The applicant has conducted extensive pharmaceutical development using design of experiments*

(DOE) as the tool. Through those experiments and data analysis, as well as the risk assessment based on the investigation outcomes described in NDA 203188 for 150 mg tablets (b) (4) *composition and manufacturing process with the granules, the criticality of the material attributes and process parameters are assessed, and the design spaces and normal operational ranges (NOR) are established. Adequate in-process and material controls are in place. The manufacturing process is robust, capable of consistently producing quality drug product when operated within the design space and NOR.*

Two of the more critical quality attributes for the drug product are dissolution and physical form. The biopharm team recommended approval of this NDA from their perspective. The desired physical form of the drug substance Ivacaftor is (b) (4)

The proposed drug product specification is acceptable. The attributes, acceptance criteria, and analytical methods are the same as those for the 150 mg tablets. The lower strengths of this product do not affect the pertinent threshold for impurity/degradant controls as per ICHQ3B. The proposed testing strategy (certain attributes are tested on the bulk granules instead of the content in the packet) was agreed upon by the Agency during EOPII meeting.

The drug product is chemically and physically stable under the proposed storage conditions. Release data from multiple batches manufactured by the commercial process met the proposed specification. No impurity/degradant was detected at above the identification threshold both at release and during stability study. During the EOPII meeting the Agency agreed that the bracketing (b) (4) *strengths of drug product when manufactured using the same commercial process and packaged in the same commercial container/closure system could be used for stability study in lieu of the to be marketed 50 mg and 75 mg strengths. The applicant therefore provided 24 months of long term stability data from developmental batches (manufactured using the same commercial process and packaged in the commercial container/closure system), 12 months long term, and 6 months of accelerated stability data from 6 registration batches (three each from* (b) (4) *mg and 75 mg) to support the proposed shelf life of 24 months. All stability data met the specification. No significant trend (>5%) is observed through 12 month time point for all the testing attributes,* (b) (4) *The requested shelf life is granted. In-use stability study conducted as per the Agency's recommendations during EOPII meeting demonstrates that the drug product remains chemically and physically stable within one hour after mixing with the common food.*

The primary container closure system for ivacaftor granules will be a printed, foil laminate packet (b) (4)*. Fifty six packets (for each strength) are packed into a carton. CFR citation for direct food contact is provided for the components of the primary container/closure system.*

The following comments regarding the labeling and container labels should be conveyed to the review team.

1. *Indicate the drug product strength in the Highlights of Prescription section of the package insert as per 21CFR201.57(a)(8).*
2. *Change the color scheme of the inner wallet, carton, and stick pack for 50 mg and 75 mg strengths such that they are adequately distinguishable.*
3. *Increase the font of the established name to be at least half of that for the proprietary name for all container labels as per 201.10(g)(2)*
4. *Clearly indicate the location for Lot number and expiration date on all container labels as per 21CFR201.17 and 21CFR201.18.*

B. Description of How the Drug Product is Intended to be Used

KALYDECO (ivacaftor) Granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed to ensure delivery of the entire dose. Once mixed, the product has been shown to be stable for one hour, and therefore should be consumed during this period. Some examples of appropriate soft foods or liquids may include puréed fruits or vegetables, yogurt, applesauce, water, milk, or juice. This description is included in the package insert.

C. Basis for Approvability or Not-Approval Recommendation

NA

III. Lifecycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach in control strategy**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Appearance	• inadequate (b) (4)	L	(b) (4)	L	
Appearance	parameter ranges may lead to integrity problems with				

	(b) (4)		(b) (4)		
Identification	• incorrect (b) (4) material accepted (incorrect API formulated)	L	ID is tested on the bulking granules and finished product	L	
Assay	• assay/purity of input ivacaftor (b) (4) and excipients (b) (4) • assay of bulk granules differs from assay or filled packets	L	(b) (4) established through DOE. The manufacturing process is adequately validated.	L	
Degradation Products	• poor packet seal integrity • high degradant levels in the ivacaftor (b) (4) • compatibility of ivacaftor with excipients • degradation of APIs on stability	L	The drug product is chemically quite stable. Controls for material attributes and manufacturing process and container/closure system provide adequate assurance that no degradation product was detected at	L	

			above the identification threshold at release and during stability study.		
Dissolution (ivacaftor, BCS class II or IV)	• variability of input materials (e.g., bulk density of ivacaftor (b) (4) (b) (4) • dissolution of bulk granules differs from dissolution of granules in filled packets	M	This attribute was thoroughly investigated under variable conditions during pharmaceutical development (DOE). Controls for material attributes and manufacturing process and container/closure system provide adequate assurance that dissolution acceptance criteria was met at release (bulk granules) and during stability study (in the packet).	L	Dissolution should be carefully evaluated for any post approval change in critical material attributes, manufacturing process controls, and container/closure system.
Uniformity of Dosage Units (ivacaftor, high drug load)	• high or low assay of ivacaftor (b) (4) (b) (4)	L	Controls for material attributes and manufacturing process provide adequate assurance that the acceptance criterion for uniformity of dosage units was met for all batches at release. (b) (4) bulk density	L	

	(b) (4)		(b) (4) were included as variables in the experimental designs.		
Microbial limits	• (b) (4) content increasing above acceptance criteria • quality of input materials	L	Controls for material attributes and manufacturing process and container/closure system provide adequate assurance that the acceptance criterion for (b) (4) was met for all batches at release and during stability.	L	
Physical form (ivacaftor)	• physical forms of drug substances are potentially altered during processing	M	This attribute was thoroughly investigated under variable conditions during pharmaceutical development (DOE). The drug product is physically stable under the current manufacturing condition and in the proposed container/closure system. Controls for material attributes (b) (4)	L	Physical form should be carefully evaluated for any post approval change in critical material attributes, manufacturing process controls, and container/closure system.

			manufacturing process and container/closure system provide adequate assurance that no undesired (b) (4) were detected at release and during stability		

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature: See Panorama

B. Endorsement Block: See Panorama

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

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 207925 Received Date: 17-SEP-2014

ONDQA-BIOPHARMACEUTICS A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	Not Applicable.
6.	Is there information provided to support the biowaiver request?		x	Not Applicable.
7.	Does the application include an IVIVC model?		x	Not Applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?	x		(b) (4) [redacted]
9.	Is information on mixing the product with foods or liquids included?		x	The draft labeling states "The entire contents of each packet of granules should be mixed with one teaspoon (5 mL) of age-appropriate soft food or liquid and completely consumed. 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 foods or liquids may include puréed fruits or vegetables, yogurt, applesauce, water, milk or juice." CMC will review this issue.
10.	Is there any in *vivo* BA or BE information in the submission?	x		VX10-770-012 and VX12-770-015 will be reviewed by Clinical Pharmacology.

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**

11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

INITIAL BIOPHARMACEUTICS ASSESSMENT

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	65 rpm	900 ml	37 °C	50 mM phosphate buffer (pH 6.8) w/ 0.4% SLS

The proposed dissolution acceptance criterion is:

Acceptance Criterion
Q = (b) (4)% at 20 min

RECOMMENDATION:
The ONDQA Biopharmaceutics team has reviewed NDA 207-925 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

CMC FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 207925 Received Date: 17-SEP-2014

	Parameter	Yes	No	N/A	Comment
14.	Is the CMC section organized adequately?	X	☐	☐	
15.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
16.	Are all the pages in the CMC section legible?	☐	☐		All pages examined for production of this IQA/filing review were legible.
17.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	☐	Information regarding the determination of the target granule fill count has been provided in the manufacturing process development section; however, the adequacy will be a review issue (see CMC EoP2 meeting minutes). For biopharmaceutics related items, see above.

B. FACILITIES*					
	Parameter	Yes	No	N/A	Comment
1	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	See form 356h
1	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	☐	☐	X	

2	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☐	X	☐	The ivacaftor (b) (4) used to prepare the dosage form is referenced to the applicant's NDA 203188.
2	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

2	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
2	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
24.	Has an environmental assessment report or categorical exclusion been provided?	X	☐	☐	Exclusion requested as per 21 CFR 25.15 and 25.31(b); Applicant also claims that they know of no extraordinary circumstances regarding the EA.

D. MASTER FILES (DMF/MAF)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
25.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X	☐	☐	Refer to table of DMF information above.

E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
26.	Does the section contain a description of the DS manufacturing process?	☐	X	☐	The ivacaftor drug substance is formulated into the drug product from the ivacaftor (b) (4) of NDA 203188.
27.	Does the section contain identification and controls of critical steps and intermediates of the DS (in process parameters?	☐	X	☐	See comment for 26 above.
28.	Does the section contain information on impurities?	☐	X	☐	See comment for 26 above.
29.	Does the section contain information regarding the characterization of the DS?	☐	X	☐	See comment for 26 above.
30.	Does the section contain controls for the DS?	☐	X	☐	See comment for 26 above.
31.	Has stability data and analysis been provided for the drug substance?	☐	X	☐	See comment for 26 above.
32.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	X	☐	See comment for 26 above.
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	X	☐	See comment for 26 above.
34.	Does the section contain container and closure information?	☐	X	☐	See comment for 26 above.

F. DRUG PRODUCT (DP)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
35.	Does the section contain quality controls of excipients?	X	☐	☐	
36.	Does the section contain information on composition?	X	☐	☐	
37.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X	☐	☐	
38.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X	☐	☐	
39.	Is there a batch production record and a proposed master batch record?	X	☐	☐	See R. Regional Information
40.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X	☐	☐	See P.2.2
41.	Have any biowaivers been requested?	☐	☐	☐	The biopharmaceutics team has addressed any biowaiver requests *(vide supra)*.
42.	Does the section contain description of to-be-marketed container/closure system and presentations?	X	☐	☐	
43.	Does the section contain controls of the final drug product?	X	☐	☐	
44.	Has stability data and analysis been provided to support the requested expiration date?	X	☐	☐	Stability data are provided, but other than what appears to be some linear regression, there have been no detailed analyses information included.

45.	Does the application contain Quality by Design (QbD) information regarding the DP?	X	☐	☐	
46.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	X	☐	

G. METHODS VALIDATION (MV)					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
47.	Is there a methods validation package?	☐	X	☐	Method validation reports are in P.5.3, but there is no separate methods validation package.

H. MICROBIOLOGY					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
48.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☐	☐		The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

I. LABELING					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
49.	Has the draft package insert been provided?	X	☐	☐	
50.	Have the immediate container and carton labels been provided?	X	☐	☐	
51.	Does section contain tradename and established name?	X	☐	☐	The current established name proposed is "ivacaftor granules."

A. FILING CONCLUSION					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
52.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X	☐	☐	

53.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	☐	☐	X	
54.	Are there any potential review issues identified?	☐	X	☐	
55.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	☐	X	☐	
56.	Are there any internal comments to other disciplines:	☐	☐	X	

REVIEW AND APPROVAL

This document will be signed in DARRTS by the following:

Craig M. Bertha, PhD, Acting CMC Lead
Kareen Riviere, PhD, Biopharmaceutics Reviewer
Tapash Ghosh, PhD., Biopharmaceutics Team Leader
Julia Pinto, PhD, Acting Branch Chief

{See appended electronic signature page}

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2014.10.21 10:23:47 -04'00'

Kareen Riviere -S

Digitally signed by Kareen Riviere -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kareen Riviere -S, 0.9.2342.19200300.100.1.1=2000386237
Date: 2014.10.21 10:32:28 -04'00'

Tapash K. Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2014.10.21 12:25:17 -04'00'

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2014.10.21 14:06:25 -04'00'