

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206143Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: NDA 206143
FROM: Wendy I. Wilson-Lee, Review Chemist
SUBJECT: Outcomes of Facility Inspections
DATE: 12/22/2014
CC: Alexis Childers, HFD 110 RPM; Pei-I Chu, ONDQA Reviewer; Yvonne Knight, ONDQA PM; Kasturi Srinivasachar, ONDQA CMC Lead; Olen Stephens, ONDQA Branch Chief

Facility Inspections

OC/OMPQ provided an overall recommendation of acceptable for all facilities listed for ivabradine tablets (NDA 206143) on 19-DEC-2014.

Overall Recommendation

Based on the outcomes of the facility inspections, we recommend approval of ivabradine tablets (NDA 206143) pending labeling, from a CMC perspective.

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.
Review Chemist
ONDQA DPA-I

Olen
Stephens -S

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Wendy I.
Wilson -A

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0, cn=Wendy I. Wilson -A
Date: 2014.12.22 10:36:30 -05'00'

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Vibhakar Shah, Ph.D.
2. NDA/BLA Number: 206143
Submission Date: 06/27/2014
21st C. Review Goal Date: 12/27/2014
PDUFA Goal Date: 02/27/2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	CORLANOR (Proposed)
Established or Non-Proprietary Name (USAN):	Ivabradine (INN) (Proposed USAN)
Dosage Form:	Tablet (Immediate Release)

4. SUBMISSION PROPERTIES:

Review Priority :	Original Priority (NME)
Applicant Name:	Amgen, Inc.
Responsible Organization (OND Division):	Division of Cardio-Renal Drug Products

II. Application Detail

1. INDICATION: Heart failure
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 5 mg, 7.5 mg
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes No
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			The drug substance(s) is an NME.
2.	Breakthrough Therapy Designation		X		
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		Not applicable/relevant at this stage.
7.	Rolling Submission		X		The FDA granted Fast Track designation and agreed to a "rolling" review for this NDA
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
12.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
13.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
14.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
15.	Additional notes (non-filing issue)	X		
	1. Are all sites registered or have FEI #?		X	
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		- NME - 1 st FDA evaluation for (b)(4) (FEI: (b)(4))
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion?	X		Not relevant at this stage, i.e., NDA filing stage
	Have all EERs been updated with final PAI recommendation?		X	
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PET	Design Space	Continuous Mfg	Naturally derived API
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (explain):			

Manufacturing Highlights:

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	The drug substance is a New Molecular Entity hence a PAI of the API manufacturing facility, (b) (4) is automatically triggered and recommended. The DS is highly soluble between pH (b) (4) and claimed to be (b) (4) compound

Drug Substance Manufacturing Process flow chart/diagram (see eCTD Section 3.2.S.2.2)

The drug substance, Ivabradine hydrochloride is manufactured by Oril Industrie and the flow diagram for its manufacture is reproduced from the NDA on page 5 of this review.

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, and unusual control strategy)?		X	This is a (b) (4) tablet mfg. process involving (b) (4)

Drug Product Manufacturing Process flow chart/diagram (see eCTD Section 3.2.P.3.3)

The drug product, Ivabradine tablet, will be manufactured by (b) (4) and the flow chart for its manufacturing process is reproduced from the NDA in the Figure 2 on pages 6-8 of this review. Ivabradine is intended to be marketed in 2 strengths of immediate release film coated tablets, 5 mg and 7.5 mg. The two strengths are distinguished by shape – oval versus triangular and debossing, 5 or 7.5 on one face. The commercial batch size will be (b) (4) Kg.

3. Facility-Related Risks or Complexities (e.g., number of foreign sites, large number of sites involved, etc.)

Three foreign contract manufacturing organizations are involved in the manufacture of the DS starting materials ((b) (4)), DS intermediate (b) (4) and the DS-Ivabradine hydrochloride respectively (see table on page 9).

Additional information on Manufacturing issues or Complexities

Drug Substance: None

Drug Product: None

Figure 1: Drug substance Manufacturing Process Flow Diagram (see eCTD Sec 3.2.S.2.2)

Figure 1. Flow Diagram

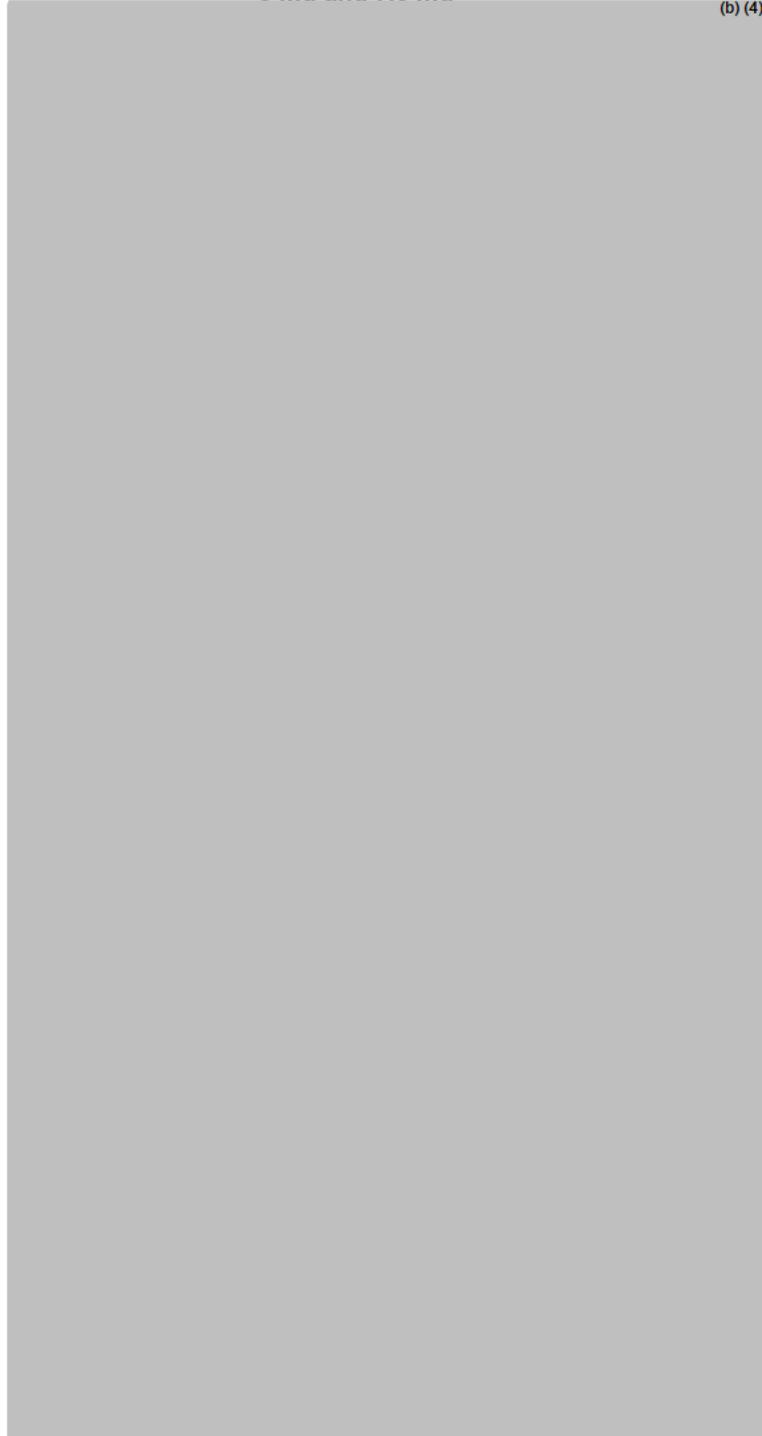
(b) (4)



The current commercial batch size for Ivabradine hydrochloride is (b) (4) Kg.

Figure-2: Drug Product Manufacturing Process Flow Diagram (see eCTD Sec 3.2.P.3.3)

**Figure 1. Manufacturing Process Flow Diagram, Ivabradine Tablets,
5 mg and 7.5 mg**



V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no)	YES
At this time, is a KTM warranted for any PAI? (yes – site / no):	NO
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no):	NO
Comments for 74 Day Letter	None
1.	
2.	
3.	

REVIEW AND APPROVAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIBHAKAR J SHAH
12/04/2014

MAHESH R RAMANADHAM
12/04/2014



NDA 206143

Ivabradine (5mg and 7.5 mg Film Coated Tablet)

Amgen Inc.

Wendy I. Wilson-Lee, Ph.D. (drug substance)

Pei-I Chu, Ph.D. (drug product)

Office of New Drug Quality Assessment DPA1

For Division of Cardio renal Drug Products

Review of Chemistry, Manufacturing, and Controls

Chemistry Review Section

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Chemistry Review Section

Chemistry Review Data Sheet

1. NDA 206143
2. REVIEW # 1
3. REVIEW DATE: November 26, 2014
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D. (drug substance)
Pei-I Chu, Ph.D. (drug product)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N.A.	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	October 3, 2014
Amendment	August 11, 2014
Amendment	July 18, 2014
Original	June 27, 2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Amgen Inc.
Address:	One Amgen Center Drive, Thousand oaks, CA 91320-1799
Representative:	Christine Kubik, Senior Manager, Regulatory Affairs
Telephone:	301-944-5364

8. DRUG PRODUCT NAME/CODE/TYPE: N/A

- a) Proprietary Name: Corlanor
- b) Non-Proprietary Name (USAN): Ivabradine
- c) Code Name/# (ONDC only): S-16257-2
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1

Chemistry Review Section

- Submission Priority: P

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

10. PHARMACOL. CATEGORY: PAH

11. DOSAGE FORM: Film Coated Tablet

12. STRENGTH/POTENCY: 5mg, 7.5mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

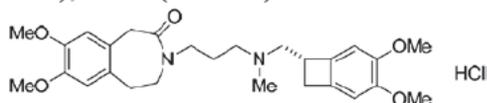
Not a SPOTS product

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

Chemical Name: 3-(3-(((7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl)methyl amino)propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride

Mol. Formula: $C_{27}H_{36}N_2O_5$ (free base); $C_{27}H_{36}N_2O_5 \cdot HCl$ (salt)

Mol. Weight: 468.593 (free base); 505.1 (HCl salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Section

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	24-SEP-2014	
	II		1	Adequate	06-OCT-2014		
	II		1	Adequate	08-OCT-2014		
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	III		4			Sufficient information in application	
	II		4			Sufficient information in application	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Section

6 – DMF not available

7 – Other (explain under “Comments”)

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Commercial

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Shift Study is acceptable, other study showed inconsistent finding	11/17/2014	Steve Bai
EES	TBD		Office of compliance
Pharm/Tox	Acceptable	11/25/2014	Jean Wu
Biopharm	Acceptable	11/19/2014	Sandra Suarez
LNC	NA	NA	NA
Methods Validation	Pending		Michael Trehy
OPDRA	NA	NA	
DMEPA	Acceptable with recommendation	11/25/2014	Janine Stewart
EA	NA	NA	NA
Microbiology	Acceptable	06/06/2014	Bryan S. Riley

Chemistry Review Section

The Chemistry Review for NDA 206143**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 206143 has been reviewed for the chemistry, manufacturing, and controls of the drug product section. It is determined that the CMC information provided for the drug substance and drug product is adequate. Office of Compliance has yet to inspect the drug substance, drug product and packaging facilities. The drug substance and drug product CMC sections of this NDA are recommended for approval pending acceptable inspection results.

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

None as per this review.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s)****Drug Substance**

Ivabradine is a novel, selective hyperpolarization-activated, cyclic nucleotide-gated channel inhibitor of the cardiac f-current. (b) (4)

Ivabradine HCl is a white to slightly yellow powder that is highly soluble across the physiological pH range. (b) (4) manufactures the drug substance in a six step, (b) (4)

The proposed drug substance regulatory specification controls the description (visual); identification (FTIR, HPLC, chiral HPLC); assay (titration); (b) (4) content (titration); impurities (HPLC); (b) (4) content (ICP-OES); residual solvents (GC); undesired isomer (HPLC), water content (KF) optical rotation, heavy metals; and residue on ignition. Two mutagenic impurities – (b) (4) – were identified as process impurities. The manufacturing process controls the levels of these impurities below the threshold of toxicological concern based on the proposed maximum daily dose. As such, (b) (4) are not controlled in the final drug substance. All drug substance analytical methods are appropriate and validated (b) (4) for their intended use. The (b) (4) is specific for the desired (b) (4). Based on stability data, the assigned retest period is (b) (4) months when stored (b) (4)

Chemistry Review Section

Drug Product

The drug product is intended to be marketed in 2 strengths of immediate release film-coated tablet for oral use. The 5 mg strength is presented as salmon colored, oval shaped, film-coated tablet, scored on both edges, debossed with "5" on one face and bisected on the other face. The 7.5 mg strength is presented as salmon colored, triangular shaped, film-coated tablet, debossed with "7.5" on one face and plain on the other face. The different dose strengths have the same tablet weight. The qualitative compositions of the two strengths are similar with differences (b) (4)

Excipients used in the tablet formulation include lactose monohydrate, maize starch, maltodextrin, magnesium stearate, colloidal silicon dioxide and (b) (4) polyethylene glycol 6000. All excipients used in the tablet core are compendial excipients. Even though the (b) (4) coating material is not compendial, all the ingredients in the (b) (4) formulation are USP/NF/Ph. Eur. grade.

The manufacturing process development depends heavily on prior knowledge gained at (b) (4) where consistent process unit operations have been demonstrated across multiple scales. Process set-points developed by (b) (4) for ivabradine tablets have been translated into operating conditions for stability batches manufactured at (b) (4) the commercial site for the US market. (b) (4) was chosen for the manufacturing process because (b) (4)

The proposed drug product specifications include standard tests for an immediate release dosage form, i.e. identification, assay, degradation products, content uniformity and microbial limits. Disintegration is proposed instead of dissolution testing. Five degradation products/process impurities are specified at levels equal to or below the qualification threshold of (b) (4)%. The primary packaging components of container closure system used for commercial distribution are (1) (b) (4) sealed blister pack composed of a (b) (4) sheet and a 20 um thick aluminum foil, (2) 45 cc opaque white high density polyethylene (HDPE) bottles closed with aluminum foil lined heat induction seals and (b) (4) closures (b) (4) The drug product stability program includes 18 stability batches stored at 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH conditions. Up to 36 months of stability data in the blisters have been provided. However, only 12 months of stability data in the bottle are generated. There were no changes in any of the product quality attributes noticed in the stability data provided. Based on available stability data, a 36 month shelf life will be granted for the blister package. A 24-month shelf life will be granted for the bottle package.

Chemistry Review Section

Drug Product Lifecycle Knowledge Management

From Initial Quality Assessment (IQA)			Review Assessment		
Product Attribute/CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation approach in control strategy	Final Risk Evaluation	Lifecycle Considerations/comments
Physical Stability (solid state)	(b) (4)	Low	(b) (4)	Acceptable	(b) (4)
Functionally scored tablet (5mg) Content Uniformity		Medium		Acceptable	Ensure the same in-process parameters will be used for manufacturing the tablets
Functionally scored tablet (5mg) Friability		Medium		Acceptable	Ensure the same in-process parameters will be used for manufacturing the tablets
Functionally scored tablet (5mg) Dissolution		Medium		Acceptable	Ensure the same in-process parameters will be used for manufacturing the tablets
Assay, Chemical Stability		Low		Acceptable	Stability data need to be re-evaluated if there is any change in drug substance (b) (4) process.
Content Uniformity		Medium		Acceptable	Evaluate if changes in manufacturing conditions will impact CU
Microbial Limits		Low	Tested on release and stability	Acceptable	The manufacturing site should follow c-GMP requirement
Disintegration		Low	BCS1 class	Acceptable	(b) (4) should be controlled to ensure that the drug has adequate disintegration time

*Risk ranking is FMECA based and applies to product attribute CAQ. Low ≤25 RPN, Med =25-60 RPN, High >60RPN

Chemistry Review Section

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

Corlanor (ivabradine) is indicated to reduce the risk of (b) (4) or hospitalizations for worsening heart failure in patients with chronic heart failure (b) (4) in sinus rhythm with heart rate ≥ 70 beats per minute (bpm), in (b) (4) maximally tolerated doses of beta blockers or when beta blocker therapy is contraindicated (b) (4). Starting dose is 5 mg tablet twice daily. After 2 weeks of treatment, the dose should be reviewed and adjusted depending on heart rate.

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval of NDA 206143 from a Product Quality perspective, pending facility inspection results by Office of Compliance.

II. Administrative**A. Reviewer's Signature**

Wendy I. Wilson-Lee, Ph.D.
Pei-I Chu, Ph.D.

B. Endorsement Block

Chemist Name:	Wendy I. Wilson-Lee, Ph.D. and Pei-I Chu, Ph.D.
Chemistry CMC Lead:	Kasturi Srinivasachar, Ph.D.
Chemistry Branch Chief :	Olen Stephens, Ph.D.
Chemistry Project Manager :	Yvonne Knight

C. CC Block

Orig. NDA-206143

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Chemistry Review Section

Wendy I.
Wilson -S

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Wilson -S
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00396790, cn=Wendy I. Wilson
-S
Date: 2014.12.02 09:38:56
-05'00'

Signing as Drug Substance Reviewer and on behalf of Pei-I Chu, Ph.D., Drug Product Reviewer

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
Date: 2014.12.02 09:41:47 -05'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Pei-I Chu, Ph.D., CMC Reviewer
Kasturi Srinivasachar, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Peii.Chu@FDA.HHS.GOV
Phone: (301)-796-3887
FAX: (301)-796-9747

Through: Olen Stephens

And Phone: (301)-796-3901
Youbang Liu
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 206143

Name of Product: Ivabradine 5mg and 7.5mg film coated tablet

Applicant: Amgen

Applicant's Contact Person: Christine Kubik

Address: One Amgen Center Drive, Thousand oaks, CA 91320-1799

Telephone: 301-944-5364 Fax: 8054801330

Date NDA Received by CDER: **06/27/2014**

Submission Classification/Chemical Class: 0

Date of Amendment(s) containing the MVP:

Special Handling Required: No

DATE of Request: **08/11/2014**

DEA Class: N/A

Requested Completion Date: **10/11/2014**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **02/27/2015 (Priority)**

Paper

Electronic

Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA # 206143
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
To be provided by applicant				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1, 3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1, 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3, 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms				3.2.S.4.4, 3.2.P.5.4
Other:				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
	Drug substance assay ((b) (4))	3.2.S.4.2	0	
	Drug substance impurities (HPLC)	3.2.S.4.2	0	
	Drug substance (b) (4) content (HPLC)	3.2.S.4.2	0	
	Drug product assay and impurity (HPLC)	3.2.P.5.3	0	
			0	
Additional Comments: The applicant did not include method validation package in the original filing. A request has been sent to include the package in P.3.2.R.				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

PEI-I CHU
08/14/2014

OLEN M STEPHENS
08/14/2014

CMC and Biopharmaceutics

NDA 206143

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206143

2. DATES AND GOALS:

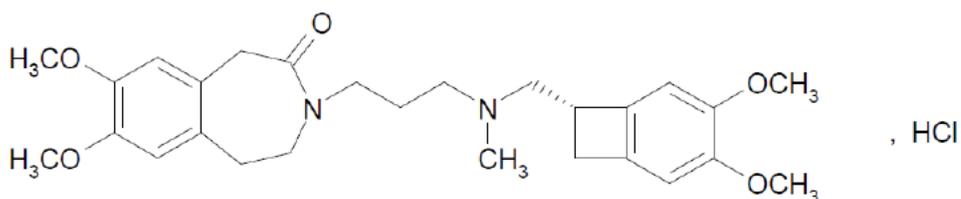
Letter Date:	30-Apr-2014 (CMC and Non-Clinical Only—Rolling submission; 27 June, 2014 complete NDA)
Filing:	26-Aug-2014
Filing 74 Day Issues:	09-Sep-2014
PDUFA Goal Date:	TBD

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	CORLANOR (Proposed)
Established or Non-Proprietary Name (USAN):	Ivabradine (INN) (Proposed USAN)
Dosage Form:	Tablets, Immediate release
Route of Administration	Oral
Strength/Potency	5 mg and 7.5 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Heart failure

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h):

Amgen, Inc.



7. SUBMISSION PROPERTIES:

Review Priority:	TBD (Priority requested by Amgen)
Submission Classification (Chemical Classification Code):	Type 1
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DCRP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	
Methods Validation	X		MV Package not submitted
Environmental Assessment		X	Categorical exclusion
CDRH		X	
Other	X		Microbiology

9. QUALITY REVIEW TEAM:

Discipline	Reviewer
CMC	Wendy Wilson, Ph.D (DS), Pei-I Chu, Ph.D. (DP)
Biopharmaceutics	Sandra Suarez Sharp, Ph.D.
Biopharmaceutics TL (Secondary)	Angelica Dorantes, Ph.D.
Microbiology	Brian Riley, Ph.D.
Facilities	Vibhakar Shah, Ph.D.



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Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?
Yes
CMC Filing Issues: None

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?
Yes
CMC Comments for 74-Day Letter: Submit MV Package in 3.2.R

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes
Biopharmaceutics Filing Issues:
None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes
Biopharmaceutics Comments for 74-Day Letter:
Include comments A, B, C, D, and E listed in pages 11 to14 of this document.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes
Microbiology Filing Issues: None. Microbiology review complete and approval recommended from Microbiology perspective

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Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	DOEs to establish process parameters	No	

CMC Summary of Critical Issues and Complexities

Initial Assessment of Risk based on DS Properties and DP Formulation/Process

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	FACTORS AFFECTING CQA	O	S	D	FMEC A RPN	Comments
Physical stability (solid state)	(b) (4)	3	2	3	18	(b) (4)
Functionally scored tablets (5 mg) Content uniformity	(b) (4)	4	3	5	60	(b) (4)
Functionally scored tablet (5 mg) Friability	(b) (4)	3	3	5	45	(b) (4)
Functionally scored tablets (5 mg) Dissolution	(b) (4)	3	2	5	30	(b) (4)
Assay, Chemical Stability	(b) (4)	2	3	3	18	(b) (4)
Content Uniformity	(b) (4)	3	3	4	36	(b) (4)
Microbial limits	(b) (4)	1	3	1	3	(b) (4)
Dissolution	(b) (4)	1	3	1	3	(b) (4)
Disintegration	(b) (4)	1	3	1	3	(b) (4)

RPN < 25 is considered **low** risk; RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.

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O is occurrence; S is severity; D is detectability

Drug Substance:

- BCS Class I claimed by Applicant
- One chiral center (b) (4)
- Photostable in the solid state
- Particle size not specified—not expected to impact product performance because drug is highly soluble between pH (b) (4)
- DMFs for (b) (4) intermediates –no prior review.
- Two potential genotoxins, (b) (4), not included in DS specification—justification provided.

Drug product:

- Change in manufacturing site from clinical study site to US commercial manufacturing site at (b) (4) – bridged with comparative dissolution data.
- Disintegration testing proposed for release and stability instead of dissolution.
- Stability data provided from 3 sites – 2 OUS commercial sites in (b) (4) and (b) (4) and proposed US commercial site, (b) (4). 36 months' long term data from (b) (4) sites and 6 months' data from (b) (4). (b) (4), HDPE bottle packaging data only from (b) (4). All commercial scale batches. Shelf-life of (b) (4) months proposed.
- Photostable – no special packaging required.

Quality Assessment

This is a 505(b)(1) NDA for a new molecular entity, ivabradine. Ivabradine is a small molecule that acts as a selective and specific heart rate lowering agent and therefore of potential therapeutic value for patients with chronic heart failure. This application is based solely on foreign clinical data and consequently no IND application is associated with it. The FDA granted Fast Track designation and agreed to a “rolling” review for Ivabradine’s NDA. Complete Modules 3 and 4 (CMC and Non-Clinical) were submitted early and the rest of the application was submitted on 27 June, 2014.

Only one meeting was held with Amgen, a CMC specific meeting on December 6, 2013. The major issue agreed to at this meeting was that a change in drug product manufacturing site would not require a bioequivalence study. Amgen stated that release and 3 months of accelerated stability data would be submitted for the commercial drug product manufacturing site ((b)(4)) in addition to the stability data for the registration batches from (b)(4) . The other major issue discussed was the acceptability of the proposed starting materials in the drug substance synthesis. The Applicant was informed that the compounds designated (b)(4) were not acceptable as starting materials in view of their (b)(4) . Amgen was advised to choose appropriate (b)(4) compounds and justify their suitability for this purpose.

Drug Substance: Ivabradine hydrochloride is a white to slightly yellow powder, mp 192°C. It is freely soluble in water. It is a small molecule with one chiral center. (b)(4)

(b)(4) with the S absolute configuration (b)(4)

(b)(4) The drug substance is manufactured by (b)(4) but there are two other manufacturing sites for the intermediate (b)(4) and the starting materials – (b)(4)

(b)(4) The (b)(4) pathway is stated to be unchanged from the initial development and pre-clinical batches except for modifications which the Applicant considers minor. The current commercial batch size is (b)(4) Kg.

Twelve potential impurities have been identified, 10 of which are both process related and degradation products, and the remaining two are only potential degradation products. There is a section dealing with potential genotoxic impurities that could be theoretically present in the drug substance. 36 impurities with structural alerts were screened by in silico analysis (Derek) and only two were found to have a structural alert for mutagenicity – (b)(4) . A rationale for not including these two impurities in the drug substance specifications has been provided.

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The specifications cover the customary attributes, description, identification, assay, organic impurities, (b) (4), water, sulfated ash, heavy metals, (b) (4) content. Batch analysis data have been provided for 3 validation batches as well as 2 batches used at the proposed commercial drug product manufacturing site.

Stability data have been generated on 8 commercial batches at ICH long term and accelerated storage conditions. 36 months of data are available at 25° C/60% RH and 30° C/70% RH in addition to 6 months of data at 40° C/75%RH for all batches except two where 24 months of data at 25° C/60 % RH and 6 months of data at 40° C/75% RH are provided. No trends have been observed in these studies and there are no changes in any stability parameter. A re-test period of (b) (4) months is proposed. Ivabradine HCl was also shown to be photostable (b) (4). In solution, it did undergo degradation under forced conditions of acid, base and light.

Drug Product: Ivabradine is intended to be marketed in 2 strengths of immediate release film coated tablets, 5 mg and 7.5 mg. The two strengths are distinguished by shape - oval versus triangular and debossing, 5 or 7.5 on one face. In addition, the 5 mg strength is scored on both edges and has a bisect on the other face whereas the 7.5 mg strength is plain. Standard compendial excipients are used in the manufacture of the core tablets – lactose monohydrate, maize starch, maltodextrin, magnesium stearate and colloidal silicon dioxide. Except for (b) (4) are used in the same amounts for the 2 strengths. The amount of lactose monohydrate is adjusted so that the core tablet weight is 100 mg for both strengths. The film coating is composed of (b) (4) and compendial grade PEG 6000. (b) (4)

. Excipient (b) (4) compatibility studies showed that using a (b) (4) produced satisfactory long term stability at 30° C/60%RH (b) (4)

During clinical development several oral formulations were used including a capsule and an earlier tablet formulation for Phase 1 and 2 studies. The final formulation, used in Phase 3 studies, and intended for marketing differs in several respects: (b) (4)

The drug product manufacturing site will change from the current site, (b) (4) to the proposed (b) (4) commercial manufacturing site, (b) (4). In vitro dissolution comparisons in 3 media have been performed and show that more than (b) (4)% of the label amount is dissolved in 15 min for both strengths in all 3 media.

The manufacturing process development depends heavily of prior knowledge gained at (b) (4) where consistent process unit operations have been demonstrated across multiple scales. Process set-points developed by (b) (4) for the manufacture of ivabradine have been translated into operating conditions for stability batches manufactured at (b) (4) was chosen for the manufacturing process because (b) (4) and the equipment for this operation is readily available at developmental and commercial scales.

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The optimization of the manufacturing process at (b) (4) followed a stepwise (b) (4) strategy from (b) (4) L. DoEs carried out at the (b) (4) L scale demonstrated process robustness (b) (4). DoE results showed that the (b) (4) both 5 mg and 7.5 mg strengths ((b) (4)) produces acceptable tablet properties like content uniformity, disintegration, dissolution and assay. Based on the process developed at (b) (4) a technical transfer was completed to (b) (4), the site chosen for commercialization of ivabradine for the US market. Stability batches were manufactured at (b) (4) and the manufacturing process was further refined based on risk assessment to address areas requiring additional development to improve process consistency.

The commercial batch size will be (b) (4) Kg and the process starts (b) (4)

The proposed drug product specifications include standard tests for an immediate release dosage form, i.e. identification, assay, degradation products, content uniformity and microbial limits. Disintegration is proposed instead of dissolution testing. Five degradation products/process impurities are specified at levels equal to or below the qualification threshold of (b) (4) %.

Batch analysis data have been submitted for numerous commercial scale batches manufactured at 3 different sites – (b) (4)

These include six recent batches (3 for the 5 mg and 3 for the 7.5 mg strengths) manufactured at (b) (4) and packaged in both blisters and bottles. Stability data have also been generated on the same batches at the 3 sites. The batches at (b) (4) were only

(b) (4) batches were packaged in (b) (4) HDPE bottles, the container closure systems proposed for marketing. 36 months of data at 25°C/60% RH and 30°C/65% RH and 6 months of data at 40°C/75% RH are available at the (b) (4) sites for 3 batches of each strength but only 6 months of data at accelerated and long term (30°C/65% RH) are provided for the proposed commercial manufacturing site at (b) (4). It is stated that the blister contact materials are the same at all 3 sites. Based on these data, a shelf-life of 36 months is proposed for (b) (4) blister (b) (4) configurations. (b) (4) fill counts for the bottles, (b) (4) 60 and 180 tablets are proposed. Disintegration instead of dissolution testing is performed as one of the tests in the stability studies.

Additional Comments: Facilities for inspection have been entered in EES. Methods Validation from St. Louis will be requested for this NME upon receipt of a MV Package.

Biopharmaceutics Assessment

Amgen seeks approval of Ivabradine for the treatment of chronic heart failure. Ivabradine was originally developed by Les Laboratoires Servier and as December 2013, it has been approved outside the United States (US) in 88 countries for the treatment of chronic heart failure and in 102 countries for the treatment of angina. The efficacy and safety of ivabradine for the proposed indication is supported primarily by the results of a single large, randomized, placebo-controlled study with support from 5 phase 2 heart failure studies conducted outside the US (foreign clinical data).

Ivabradine hydrochloride is formulated as an immediate release oral solid dosage form in strengths of 5 mg and 7.5 mg of Ivabradine as the free base equivalent. The two strengths are (b) (4) and the Applicant states that the PKs are (b) (4) over the 2.5 to 7.5 mg dose range. The 5 mg tablet is scored; CMC and dissolution data were provided to justify the bridging between splitted and non-splitted tablets. For specifics refer to the dp-development link below.

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There are two manufacturing sites for the product under review; (b) (4), which are the proposed and previous manufacturing sites, respectively. Dissolution data were submitted to support the bridging.

According to the Applicant, Ivabradine is a (b) (4) (b) (4) in healthy subjects and patients, but has a moderate bioavailability (approximately 40%) due to extensive first-pass metabolism in the gut and liver, which is independent of the oral formulations. The following data were provided to support the (b) (4)

1. The solubility of ivabradine in water is approximately 47 mg/mL (Module 3.2.P.2.1): The percentage of drug dissolved within 15 minutes was > (b) (4) % for all the formulations and strengths throughout the pH range tested (Section 4.4).
2. All the formulations tested comply with the definition of a (b) (4) "dissolving" product (Section 3.2.2).
3. An average of 93% absorption of an oral dose of [14C]-ivabradine in healthy subjects determined by the recovery of phase 1 metabolism in feces and total radioactivity in urine (Section 3.1.4.1 of Module 2.7.2). These data will be reviewed by OCP.
4. Mean oral bioavailability of 91% and 92% in clinical drug-drug interaction studies with the strong CYP3A4 inhibitors ketoconazole and josamycin, respectively (Section 3.1). These data will be reviewed by OCP.
5. Predicted Fabs of 91% from an in vitro Caco-2 permeability study that included multiple reference compounds (Module 2.6.4).

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6. Linear PK in dose-ranging studies in healthy subjects and multiple dose studies in patients (Section 3.1.1 of Module 2.7.2). These data will be reviewed by OCP.
7. Dissolution of drug product from different manufacturing sites showed comparable, very rapid dissolution of greater than (b) (4)% in 15 minutes in all dissolution media (Module 3.2.P.2.2).

During the clinical development of ivabradine, several oral formulations (b) (4) were manufactured and administered to subjects and patients, as follows:

- Hard gelatin capsule at doses ranging between 0.5 mg and 50 mg (used in the early phase I studies)
- (b) (4) (used in some clinical pharmacology and PK studies).
- Film-coated tablet formulation manufactured at doses ranging between 2.5 mg and 10 mg with a final tablet weight of (b) (4) mg (used in two phase II studies including the pivotal dose-ranging study in patients, CL2 009, and one PKH study).
- Film-coated tablet (definitive formulation manufactured at doses of 5 mg, 7.5 mg, and 10 mg with a (b) (4) weight of (b) (4) mg (used in Phase III trials and most of the Phase I and Phase II studies, namely CL1, CL2 and PKH studies). Major formulation differences were implemented to the previous film-coated tablet stated above.
- Definitive IR tablets over-encapsulated to maintain blinding conditions for clinical studies involving comparators or to achieve the targeted dose with tablet halves.

A population PK approach comprising the simultaneous modeling of ivabradine and its major active metabolite, S18982, was used for the comparison of the relative bioavailability of the different pharmaceutical formulations used throughout the clinical development program of ivabradine (capsule, experimental tablet, and over-encapsulated definitive tablet) versus the relative bioavailability of the definitive tablet used in the phase 2 and phase 3 safety and efficacy studies. These data will be reviewed by OCP.

The biopharmaceutics review will be focus on the acceptability of:

1. The data provided to support the use of disintegration testing in lieu of dissolution.
2. The data submitted to support the (b) (4)
3. The data submitted to support the manufacturing site change

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The following comments should be conveyed to the Applicant as part of the 74-day letter:

- A. Provide data demonstrating the same physicochemical properties (e.g. solubility profile, melting point, hygroscopicity, intrinsic dissolution etc.) for all the potential solid state forms of ivabradine hydrochloride drug substance. If there are clear differences in these physicochemical properties (e.g. not highly soluble in the physiologically relevant pH), then you should provide data/justification for the lack of impact of any observed differences on the bioavailability of the drug product.
- B. We acknowledge your proposal to use disintegration in lieu of dissolution testing. Note that if no data are provided to support the superior discriminating ability of disintegration over dissolution testing (see also comment C), you need to provide data supporting an adequate (discriminating) dissolution method for your proposed product.
- C. Provide data showing the superior discriminating capability of disintegration testing. The testing conducted to demonstrate the discriminating ability of this test should compare the dissolution profile and disintegration time of the drug product manufactured under target conditions vs. aberrant products intentionally manufactured with meaningful variations (i.e., +/-10-20% outside established specification ranges) for the most critical formulation and manufacturing parameters.
- D. Provide disintegration values of all the batches tested in pivotal phase 3 clinical trials.
- E. In order to facilitate the review of the (b) (4) provide sufficient information answering to the following questions:
 1. Determination of the Drug Substance Class
 - What are the highlights of the chemistry and physical-chemical properties of the drug substance?
 - What is the nature of the drug substance (acid, base, amphoteric, or neutral)? What is the dissociation constant(s), PKa(s) of the drug substance?
 - What is the solubility profile of the drug substance under physiological pH conditions (i.e., pH range (b) (4) at 37°C in aqueous media)?

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- Was the buffer solution's pH verified after the addition of the drug substance to the buffer?
- What type of method was selected to evaluate the equilibrium solubility of the drug substance? What are the specific experimental testing conditions?
- What analytical method was used to determine the concentration of the drug substance in the selected buffers (or pH conditions)? What data support the validation of the assay?
- What are the solubility pH profile results (individual, mean, standard deviation, coefficient of variation, and graphics)?
- Is the highest dose strength of the proposed drug-product soluble in 250 ml of aqueous media over the pH range of (b) (4)?
- Is the overall solubility information supportive of a (b) (4) classification for the drug substance?
- Were five pH conditions used to define the solubility pH profile? How many replicate determinations of solubility of the drug substance at each pH condition were performed?
- What type of buffer solutions were used to define the solubility profile? What are the compositions of the buffer solutions? How they were prepared?

2. Determination of Drug Substance Permeability Class

- What approach was used to determine the permeability class of the drug substance (*i.e., in vivo mass balance or absolute BA or intestinal permeability*)? If more than one method was used to demonstrate permeability classification, what is the other(s) approach?
- For human pharmacokinetic approaches - Which approach was selected (*i.e., mass balance and/or absolute BA*)? What is the information describing the study design, methods, results, etc?
- For the intestinal permeability approaches – Which method was selected (*i.e., 1) in vivo intestinal perfusion studies in humans; 2) in vivo or in situ intestinal perfusion studies using suitable animal models; 3) in vitro permeation studies using excised human or animal intestinal tissues; or 4) in vitro permeation studies across a monolayer of cultured epithelial cells*) and what is the rationale for its selection?
- Is the drug substance being testing a passively transported drug? What is the information supporting this assumption?

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- Was the linear relationship between the dose and measures of bioavailability (*humans*) demonstrated?
- Was there a lack of dependency of the measured in vitro permeability of the test article on initial drug concentration or transport direction (*no difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction*) using a suitable in vitro cell culture method. What is the supportive information?
- For the in vivo-human perfusion studies, in vivo or in situ-animal intestinal perfusion studies or in vitro cell culture methods, how many model drugs were used? What model drugs were selected and did they represent a range of absorption values? What are the permeability values for each model drug (mean, SD, CV) and what is the permeability class of each model drug?
- What information supports the suitability of the selected method (i.e., description of the study, criteria for the selected approach, analytical method, method used to estimate the extent of absorption, (*where appropriate, efflux potential*), results (individual, mean, SD, coefficient of variation), etc.)? Were the results tabulated? Was the suitability of the selected permeability method(s) adequately demonstrated?
- What drugs were selected as low and high permeability internal standards? What is the high permeability internal standard used for the permeability classification?
- What is the information supporting the (b) (4) of the drug substance (*i.e., permeability methods permeability data on the test drug substance and internal standards (mean, SD, & CV), data supporting classification and passive transport mechanism*)?
- What is the graphic representation of the extent of absorption as a function of permeability (*mean \pm SD or 95% CI*) with low/high permeability class boundary and selected internal standard(s). What is the rank-order relationship between test permeability values and the extent of drug absorption values?
- Is the overall information supporting a (b) (4) classification for the drug substance?

3. Gastric Stability

- What is the information supporting the stability of the drug substance/drug product in the GI tract?
- What are the experimental conditions used during the gastric stability experiments?
- Were simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) used to generate the chemical stability data or human fluid? What are the compositions of the SGF and SIF solutions?

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- What is the validation information for the analytical method? What is a validated stability-indicating assay?
 - What are the SGF and SIF stability results (mean, SD, CV)? Are the results tabulated?
 - Is the overall information supportive of gastric stability?
4. Determination of the Dissolution Characteristics of the Drug Product
- What is the information describing the drug product used for dissolution testing (i.e., batch/lot No., expiry date, lot size, strength, etc.)?
 - What are the selected dissolution testing conditions (i.e., apparatus, rotation speed, dissolution media, temperature, and volume)?
 - What is the sampling schedule? Does the sampling schedule adequately characterize the complete dissolution profile? Were twelve dosage units per experiment tested?
 - What is the information supporting the validation of the dissolution methodology (robustness, etc.)?
 - What is the analytical method(s) used to determine the concentration of the drug in the dissolution samples? What is the validation information for the analytical method? Was it a validated assay?
 - Was the dissolution of the drug product characterized in three different pH media?
 - What are the compositions of the buffer solutions? How they were prepared? What are the dissolution characteristics in these media?
 - What are the dissolution results (*i.e., individual, mean, SD, CV, and graphics*) in the different media? Are the results tabulated? Are the dissolution profile data reported in percent of label claim?
 - Is the drug product showing fast dissolution in the different pH media? Is more than 85% of drug being dissolved in 15-30 minutes in each medium?
 - Does the overall dissolution data support a rapid/fast dissolving designation for the drug product?

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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				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Incomplete information in original 356 h. Amendment received
6.	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.			NA



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	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

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	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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		
10	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)

	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	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		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		
24.	Does the section contain controls of the final drug product?	X		
25.	Has stability data and analysis been provided to support the requested expiration date?	X		
26.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	DoEs for setting process parameters
27.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
28.	Is there a methods validation package?		X	To be requested

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
29.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			NA



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H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
30.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Feb. 28, 2014	
	II			Mar. 24, 2014	
	II			Mar. 7, 2014	
	III			Sep. 24, 2013	
	III			Dec. 11, 2013	
	III			Sep. 24, 2013	
	III			Sep. 24, 2013	
	III			Feb. 1, 2011	
	III			Sep. 25, 2013	
	III			Feb. 13, 2014	

I. LABELING				
	Parameter	Yes	No	Comment
31.	Has the draft package insert been provided?	X		
32.	Have the immediate container and carton labels been provided?	X		

Biopharmaceutics Filing Review Checklist

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

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
33.	Does the application contain dissolution data?	x		Data supporting that the product is rapidly dissolving.
34.	Is the dissolution test part of the DP specifications?		x	<p>Disintegration testing is being proposed in lieu of dissolution testing. The following data were provided:</p> <ul style="list-style-type: none"> • Solubility across the range of physiologically relevant pH • Dissolution in three different media • The Applicant claims that a correlation between dissolution and disintegration has been established; however, no data were provided. <p>For details see \CDSESUB1\evsprod\NDA206143\0014\m3\32-body-data\32p-drug-prod\ivabradine-tablet\32p5-contr-drug-prod\32p56-justif-spec</p>
35.	Does the application contain the dissolution method development report?		x	
36.	Is there a validation package for the analytical method and dissolution methodology?		x	
37.	Does the application include a biowaiver request?		x	
38.	Are there adequate data supporting the waiver?		x	
39.	Does the application include an IVIVC model?		x	

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J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
40.	Is information such as BCS classification mentioned, and supportive data provided?	x		A claim of this product being a BCS Class 1 is included (refer to the following link for supporting data \\CDSESUB1\evsprod\NDA206143\0017\m2\27-clin-sum).
41.	Is information on mixing the product with foods or liquids included?		x	
42.	Is there any <i>in vivo</i> BA or BE information in the submission?		x	
43.	Are there any manufacturing changes implemented to the biobatch/clinical trial formulation?	x		The product has been manufactured in two sites; (b) (4) which are the proposed and previous manufacturing sites, respectively (\\CDSESUB1\evsprod\NDA206143\0017\m2\27-clin-sum).
FILING CONCLUSION				
44.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?		x	
45.	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		
46.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	x		
47.	Are there any potential review issues identified?	x		Refer to Biopharmaceutics comments in pages 9-14 of this document.



This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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