CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208434Orig1s000

CHEMISTRY REVIEW(S)

NDA 208434
Review #1, Addendum
Review Date: December 02, 2015

Drug Name/Dosage Form	Alecesna (alectinib)
Strength	150 mg
Route of Administration	Oral Capsule
Rx/OTC Dispensed	Rx
Applicant	Hoffman-La Roche Inc.
US agent, if applicable	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Facility	Zhong Li	OPQ/OPF/DIA/BI

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ASSESSMENT OF THE FACILITIES

This is an addendum to the **Overall Quality Assessment** for NDA 208434 that was filed in the Panorama review platform on **November 6, 2015**. This addendum provides an updated and final assessment of the Drug Substance and Drug Product primary stability testing facilities (see: ***Questions #34 & #35, Overall Quality Assessment***) as well as a final Overall Facility Review Assessment. All other Drug Substance and Drug Product facilities evaluation was documented in the 11/6/2015 review and since it was complete, is not reproduced here.

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

34. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Chugai Pharmaceutical Co., Ltd.	3002926698	DS Registration Stability Testing	No FDA inspection history	PAI Recommended and conducted	Acceptable Based on PAI & DO Recommendation
Chugai Pharma Manufacturing, Co., Ltd. (CPMC)	3004109596	DS Registration Stability Testing (MLT)	No FDA inspection history	PAI Recommended and conducted	Acceptable Based on PAI & DO Recommendation

Reviewer's Assessment:

Chugai Pharmaceutical Co., Ltd. (FEI 3002926698)

The site is responsible for registration stability testing of drug substance. See Question 35 in this review for assessment.

Chugai Pharma Manufacturing Co., Ltd. (FEI 3004109596)

The site is responsible for registration stability testing of drug substance. See Question 35 in this review for assessment.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

35. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Chugai Pharmaceutical Co., Ltd.	3002926698	DP Registration Stability Testing	No FDA inspection history	PAI Recommended and conducted	Acceptable Based on PAI & DO Recommendation
Chugai Pharma Manufacturing, Co., Ltd. (CPMC)	3004109596	DP Registration Stability Testing	No FDA inspection history	PAI Recommended and conducted	Acceptable Based on PAI & DO Recommendation

Reviewer's Assessment:

Chugai Pharmaceutical Co., Ltd. (FEI 3002926698)

The site is responsible for registration stability testing of the Alectinib drug product. (The firm is not responsible for performing stability testing of commercial batches of the drug product.) The firm has no FDA inspection history in FACTS. A pre-approval coverage of NDA 208343, Alectinib, was recommended by OPF/DIA.

The PAI was conducted on 11/2 & 4-6, 2015. This abbreviated pre-approval and CGMP inspection was conducted under CPGM 7356.002 Drug Manufacturing Inspections and 7346.832 Pre-Approval Inspection/Method Validation, specifically for NDA 208343, Alectinib. Three systems of drug manufacturing were covered: Quality; Facilities and Equipment; and Laboratory Controls. Production and Processing, Materials and Packaging and Labeling were not covered during this inspection. The facility is performing control laboratory testing activities under profile code CTL. This was the initial FDA inspection of this facility. The profile was updated in FACTS. The inspection was conducted concurrently with inspection of the firm's chemical testing facility and manufacturing affiliate, Chugai Pharma Manufacturing Company Limited (FEI 3004109596), which is co-located on the same campus. Chugai Pharmaceutical Company Limited performed initial formulation and developmental activities of Alectinib drug product as well as 0-12M stability testing (excluding microbiological testing) and is managing the quality assurance functions. Chugai Pharmaceutical Manufacturing Company Limited (CPMC) provides microbiological and on-going physiochemical stability testing.

At the close of the inspection on 11/6/15, a two-item Form FDA 483 was issued for the following observations: 1) lack of procedures to ensure that all data is captured and reported for laboratory analysis conducted for testing of drug substances and drug

products; and 2) failure to initiate a deviation or corrective and preventative action to ensure that chemists do not delete analytical data files. Additionally, one verbal observation which was discussed during the close-out meeting, regarding ensuring that signature stamps are maintained in a secure manner. As documented on the Form FDA 483, the firm does not have adequate procedures and limitations in place to ensure that electronic data resulting from all analytical testing is maintained and unaltered. However, the firm utilizes hardcopy documentation as raw data. The inspection revealed no instances of data manipulation or fraud. The field recommended approval of the NDA.

The Form 483 observations, firm's 11/25/2015 responses, EIR, and associated exhibits were reviewed by OPF/DIA (***CMS Work # 103430***). The firm response to FDA-483 is adequate as the firm has implemented and/or proposed appropriate CAPAs to address these deficiencies. OPF/DIA concurs with the VAI recommendation and finds the firm acceptable for drug product manufacturing operations for NDA 208434, based on coverage of the CTL profile.

Chugai Pharma Manufacturing Co., Ltd. (FEI 3004109596)

The site is responsible for registration stability testing of the Alectinib drug product. (The firm is not responsible for performing stability testing of commercial batches of the drug product.) The firm has no FDA inspection history in FACTS. A pre-approval coverage of NDA 208343, Alectinib, was recommended by OPF/DIA.

The PAI was conducted on 11/2 & 4-6, 2015. This abbreviated pre-approval and CGMP inspection was conducted under CPGM 7356.002 Drug Manufacturing Inspections and 7346.832 Pre-Approval Inspection/Method Validation, specifically for NDA 208343, Alectinib. Three systems of drug manufacturing were covered: Quality; Facilities and Equipment; and Laboratory Controls. Production and Processing, Materials and Packaging and Labeling were not covered during this inspection. The facility is performing control laboratory testing activities under profile code CTL. This was the initial FDA inspection of this facility. The profile was updated in FACTS. The inspection was conducted concurrently with inspection of the firm's sister firm performing microbiological testing, Chugai Pharmaceutical Company Limited (FEI 3002926698).

At the close of the inspection on 11/6/15, a three-item Form FDA 483 was issued for the following observations: 1) lack of procedures to ensure that all data is captured and reported for laboratory analysis conducted for testing of drug substances and drug products; 2) failure to perform ID testing of incoming organisms utilized for stability testing; and 3) failure to perform timely temperature mapping and calibration for incubators and refrigerators utilized for microbial limit testing and E. coli testing. Additionally, three verbal observations which were discussed during the close-out meeting: 1) ensuring that signature stamps are maintained in a secure manner; 2) ensuring that all training is properly documented; and 3) the need to obtain certificates of analysis for control culture organisms. As documented on the Form FDA 483, the firm does not have adequate procedures and limitations in place to

ensure that electronic data resulting from all analytical testing is maintained and unaltered. However, the firm utilizes hardcopy documentation as raw data. The inspection revealed no instances of data manipulation or fraud. The field recommended approval of the NDA.

The Form 483 observations, firm's 11/25/2015 responses, EIR, and associated exhibits were reviewed by OPF/DIA (***CMS Work # 104435***). The firm response to FDA-483 is adequate as the firm has implemented and/or proposed appropriate CAPAs to address these deficiencies. OPF/DIA concurs with the VAI recommendation and finds the firm acceptable for drug product manufacturing operations for NDA 208434, based on coverage of the CTL profile.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: Acceptable

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspectional history, the pre-approval inspection, and district recommendation, the manufacturing facilities as listed for NDA 208434 are found to be acceptable.

Zhong Li, Ph.D.

Chemist, OPQ/OPF/DIA/IABI

Date: 12/06/2015

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D.

Branch Chief, OPQ/OPF/DIA/IABI

Date: 12/07/2015

Recommendation: Approval pending an 'acceptable' facilities recommendation

NDA 208434
Review #1 6-Nov-15

Drug Name/Dosage Form	Alecesna (alectinib)
Strength	150 mg
Route of Administration	Oral Capsule
Rx/OTC Dispensed	Rx
Applicant	Hoffman-La Roche Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002 Final Module Submission	6-Jul-15	All CMC
0003 Proprietary Name	9-Jul-15	ATL, DP
0006 IR Response	27-Jul-15	Facilities
0008 IR Response	30-Jul-15	OTR
0013 IR Response	19-Aug-15	DS, Process, Biopharm
0015 IR Response	26-Aug-15	Facilities
0018 IR Response	3-Sep-15	Facilities
0022 IR Response	17-Sep-15	Process
0023 IR Response	18-Sep-15	Facilities
0025 IR Response	24-Sep-15	Process
0029 IR Response	9-Oct-15	Biopharmaceutics
0033 IR Response	23-Oct-15	Facilities, Process, Biopharm

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell	OPQ/ONDP/DNDPAPI/BI
Drug Product	Rajiv Agarwal	OPQ/ONDP/DNDPI/BII
Process	Zhaoyang Meng	OPQ/OPF/DPAI/BII
Microbiology	Zhaoyang Meng	OPQ/OPF/DPAI/BII
Facility	Zhong Li	OPQ/OPF/DIA/BI
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB/BI
Regulatory Business Process Manager	Steven Kinsley	OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Olen Stephens	OPQ/ONDP/DNDPI/BII
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Rajiv Agarwal	OPQ/ONDP/DNDPI/BII

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	Active	2-SEP-2015	Adequate: Rajiv Agarwal
	Type III			Active	2-SEP-2015	Adequate: Rajiv Agarwal
	Type IV			Active	29-AUG-2012	Adequate for (b) (4) capsule: Muthukumar Ramaswamy
	Type IV			Active	29-SEP-2015	Adequate for ink: Rajiv Agarwal

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Cross referenced application	111,723	IND
EOP 1	111,723	Meeting minutes
Type B CMC	111,723	Meeting minutes
EOP 2	111,723	Meeting minutes
Pre-phase 3	111,723	Meeting minutes
CMC EOP 2	111,723	Meeting minutes
Type C Format and Content of NDA	111,723	Meeting minutes
Type B	111,723	Meeting minutes
CMC pNDA	111,723	Meeting minutes
Type B for alternative formulations	111,723	Meeting minutes
Clinical pNDA	111,723	Meeting minutes

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology	Pending	Refer to P/T review	3-Nov-15	K. Ringgold

Executive Summary

I. Recommendations

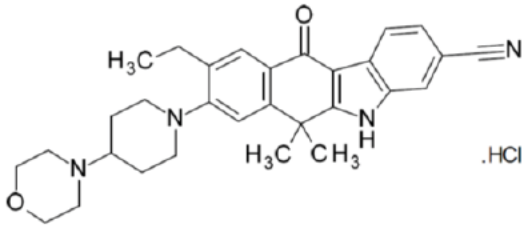
A. Recommendation and Conclusion on Approvability

NDA 208434 for Alecensa (alectinib) capsules is recommended for approval by the Office of Pharmaceutical Quality pending an adequate recommendation from the Office of Process and Facilities regarding the status of the manufacturing and testing sites. All information requests and review issues have been addressed and there are no pending review issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Summary of Quality Assessments

A. Drug Substance [Alectinib] Quality Summary



- RO5424802 (-000 is free base; [redacted] (b) (4) HCl salt; [redacted] (b) (4) HCl salt)
- $C_{30}H_{34}N_4O_2$•HCl MW: 519.08
- "Free-base": MW: 482.62
- white to yellow powder
- high melting (above 300°C with decomp.)
- pKa = 7.05 (free base)
- log P = 1.96 (1-octanol / water)
- water solubility: 0.0221 mg / mL
- in fed state simulated intestinal fluid: 0.1021 mg / mL; almost 5 fold lower in fasted state
- [redacted] (b) (4)
- [redacted] (b) (4)

INN and USAN: Alectinib

Chemical Name: 9-ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloride

Alectinib HCl is a white to yellow white powder or powder with lumps. The IUPAC name for Alectinib is 9-Ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*benzo[*b*]carbazole-3-carbonitrile hydrochloride equating to a molecular weight of 519.08 g/mol. The molecule is achiral and has a molecular formula of $C_{30}H_{35}ClN_4O_2$. The drug substance has low solubility in aqueous buffers across the entire pH range. In acidic conditions, the low solubility is attributed to the common-ion effect

with HCl buffers. Alectinib is slightly hygroscopic. (b) (4) Alectinib HCl is stored in (b) (4) not above 30 °C protected from light. An initial retest period of (b) (4) months is granted.

B. Drug Product [Alectinib Capsules] Quality Summary

On 26-JUN-2013, FDA granted Breakthrough Therapy Designation for alectinib for the treatment of patients with ALK-positive NSCLC with disease progression on crizotinib. The proposed commercial formulation is an immediate-release capsule formulation with standard excipients manufactured using conventional equipment and manufacturing processes (b) (4). A single 150 mg strength is proposed for commercialization. The recommended alectinib dose is 600 mg orally, twice a day (BID) until disease progression.

Alectinib hard capsules, 150 mg are white, Size 1 capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body. The capsule drug product are packaged in a round, white, 250 mL high-density polyethylene bottle with a child-resistant, (b) (4) screw cap and an integrated desiccant. The capsules are formulated with alectinib HCl, lactose monohydrate, hydroxypropylcellulose, sodium laury sulfate, carboxymethyl cellulose calcium, magnesium stearate, (b) (4) into a capsule shell composed of carrageenan, potassium chloride, titanium dioxide, carnauba wax, corn starch, hypromellose, and printing ink (red iron oxide, yellow iron oxide, FD&C Blue No. 2 aluminum lake, carnauba wax, white shellac, glyceryl monooleate, (b) (4)).

A 150 mg hard capsule formulation containing (b) (4) Sodium lauryl Sulfate (SLS) was developed (b) (4) This formulation was used in the Phase I/II studies NP28673 (global) and NP28761 (US and Canada), and the global Phase III study BO28984.

(b) (4) Sodium lauryl Sulfate (SLS) is (b) (4)% of the drug strength, but only (b) (4)% of the total capsule weight. This formulation was used in the Phase 3 clinical trial. The amount of SLS (b) (4)/capsule) is (b) (4) approved by the FDA. Since the dose is 1200 mg/day, this will account for (b) (4) of SLS intake each day. The acceptability of the SLS exposure is deferred to the nonclinical and clinical reviewers.

The manufacturing process follows a (b) (4)

for this formulation and manufacturing process. The manufacturing process does not employ a design space for its control strategy.

Based on 12 months of stability data for the three stability batches and stability data for three supportive batches, an expiration period of 24 months is granted when stored in 250 mL round, 240-count white HDPE bottles with child resistant closures when stored below 30 °C and protected from light.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Alecensa
Non Proprietary Name of the Drug Product	Alectinib capsules
Non Proprietary Name of the Drug Substance	Alectinib
Proposed Indication(s) including Intended Patient Population	Indicated for treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	600 mg twice daily
Alternative Methods of Administration	None indicated in the label

D. Biopharmaceutics Considerations

1. BCS Classification: 4
   - Drug Substance: low solubility (in aqueous buffers across the physiologic pH range), low permeability (absolute bioavailability is 37%)
   - Drug Product: (b) (4))

2. Biowaivers/Biostudies
   - Biowaiver Requests - none
   - PK studies–Reviewed by OCP
   - IVIVC - none

The Division of Biopharmaceutics recommends **APPROVAL** of NDA 208-434 for Alectinib Tablets, 150 mg. The following dissolution method and acceptance criteria have been agreed upon with the Applicant and should be implemented for Alectinib Tablets, 150 mg:

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criteria
2 (Paddle) with spiral coiled sinker	100 rpm	900 ml Simulated Gastric Fluid without pepsin, pH 1.2 with 4 % Triton X-100 (polyoxyethylene[10]octylphenyl ether at 37 ± 0.5 °C	30 min: Q = (b) (4) % 75 min: Q = (b) (4) %

E. Novel Approaches None

F. Any Special Product Quality Labeling Recommendations None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature: OPQ recommendation is for approval pending "acceptable" recommendation from the facilities reviewer regarding the manufacturing and facilities status.

Olen Stephens, Ph.D.
5-Nov-15

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: 2015.11.06 09:33:12 -05'00'

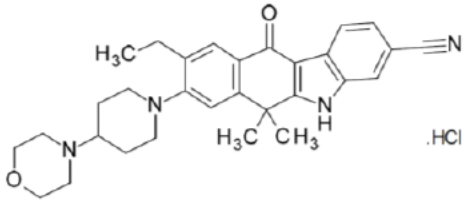
Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

Applicant's Response:



- RO5424802 (-000 is free base; (b) (4) HCl salt)
- $C_{30}H_{34}N_4O_2$•HCl MW: 519.08
- "Free-base": MW: 482.62
- white to yellow powder
- high melting (above 300°C with decomp.)
- pKa = 7.05 (free base)
- log P = 1.96 (1-octanol / water)
- water solubility: 0.0221 mg / mL
- in fed state simulated intestinal fluid: 0.1021 mg / mL; almost 5 fold lower in fasted state
- (b) (4)
- (b) (4)

INN and USAN: Alectinib

Chemical Name: 9-ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl) piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloride

Reviewer's Assessment: The compound is poorly soluble in water. Although there are (b) (4), the commercial manufacturing process produces only (b) (4) There is some conversion to the (b) (4)

2.3.S.2 Manufacture

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(b) (4)

Reviewer's Assessment: The applicant's data support the requested (b) (4) months retest period for the drug substance. The post-approval stability commitments are acceptable.

OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:
I recommend approval from the CMC drug substance perspective.
Charles F. Jewell Jr. 9/18/2015

Secondary Review Comments and Concurrence: I concur.

Kasturi Srinivasachar, Ph.D.
Acting Branch Chief, New Drug API Division
11/02/2015

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

On 26-JUN-2013, FDA granted Breakthrough Therapy Designation for alectinib for treatment of patients with ALK-positive NSCLC with disease progression on crizotinib. The proposed commercial formulation is an immediate-release capsule formulation with standard excipients manufactured using conventional equipment and manufacturing processes ((b) (4)). A single 150 mg strength is proposed for commercialization. The recommended alectinib dose is 600 mg orally, twice a day (BID).

Note: (b) (4)

2.3.P.1 Description and Composition of the Drug Product

Alectinib hard capsules, 150 mg are white, Size 1 capsules with **"ALE"** printed in black ink on the cap and "150 mg" printed in black ink on the body. The capsule drug product are packaged in a **round, white, 250 mL** high-density polyethylene bottle with a child-resistant, (b) (4) screw cap and an integrated desiccant.

Note: *3 month of site specific stability data on three batches 1403079, 1403081, and 1403082 is provided (proposed commercial batches minus **"ALE"** imprinting). The drug product is manufactured at* (b) (4) *and packaged at Roche S.p.A, Segrate.*

Components	Reference to Standards	Function	Quantity per Unit Dose (measure of wt/capsule)
Capsule Fill Mass			
Alectinib HCl	In-house specification	Active	161.33 mg[a]
Lactose Monohydrate	USP, Ph. Eur., JP		(b) (4)
Hydroxypropylcellulose	USP, Ph. Eur., JP		
Sodium Lauryl Sulfate	USP, Ph. Eur., JP		
Carboxymethylcellulose Calcium	USP, Ph. Eur., JP		
Magnesium Stearate	USP, Ph. Eur., JP		
(b) (4)			(b) (4)
Total Capsule Fill Weight	—	—	
Capsule Shell[c]		(b) (4)	
Carrageenan	USP/NF, Ph. Eur., EEC, JPE		—
Potassium Chloride	USP/NF, Ph. Eur., JP		—
Titanium Dioxide (b) (4)	USP/NF, Ph. Eur., JP		—
Carnauba Wax	USP/NF, Ph. Eur., JP		—
Corn Starch	USP/NF, Ph. Eur., JP		—
Hypromellose	USP/NF, Ph. Eur., JP		—
Printing Ink[d]	—		—
Capsule Shell Weight	—	—	(b) (4)
Total Capsule Weight	—	—	400.00 mg

Abbreviations: wt = weight; qs = quantity sufficient.

[a] 161.33 mg is the amount of alectinib HCl in the capsule, which corresponds to 150.00 mg of alectinib free base.

[b] (b) (4)

[c]

[d] The ink is composed of red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, glyceryl monooleate, (b) (4)

(b) (4)

Applicant's Response:

Reviewer's Assessment:

Two formulations, 20 mg and 40 mg capsules, were developed and used in the Phase I/II study AF-001JP (Japan only) and the dose-escalation portion (Part 1) of study NP28761. These two formulations are used in the ongoing Phase III study JO28928 conducted in Japan, and were approved for commercialization in Japan.

A 150 mg hard capsule formulation containing (b) (4) *Sodium lauryl Sulfate (SLS) was developed* (b) (4) *This formulation was used in the Phase I/II studies NP28673 (global) and NP28761 (US and Canada), and the global Phase III study BO28984. This*

150 mg hard capsule formulation is designated as the global commercial formulation.

(b) (4) The applicant states that all selected excipients are present in the formulation at concentrations well below the maximum amounts listed in the FDA's Inactive Ingredients Database (IID) for oral intake.

The specifications and other relevant CMC information for the excipient (the white capsule shell/hydroxypropyl methylcellulose and black printing ink) used in the alectinib hard capsules, 150 mg are provided in the DMF # (b) (4) and is adequate (refer to the DMF review dated 29-SEP-2015 and 29-AUG-2012 for ink and White capsule ((b) (4) , respectively.

The proposed inactive ingredient levels do not affect the safety of the proposed drug product, and the requirements outlined in 21 CFR 314.50(d)(1)(ii).

Sodium lauryl Sulfate (SLS) is (b) (4) % of the drug strength or it is about (b) (4) % (minus shell weight) of the formulation. If the weight of the capsule shell is included (as the IID does), the weight of the SLS (b) (4) % /capsule. This formulation is used in the Phase 3 clinical trial. The amount of SLS ((b) (4) /capsule) is (b) (4) approved by the FDA. Since the dose is 600 mg/day, this will account for (b) (4) of SLS intake every day.

However, the total amount of SLS ((b) (4) /day) remained constant throughout of the product development (using lower strength capsules) and it appears that CMC deemed that this amount of SLS is appropriate (refer to the CMC review of the IND 111723 dated 28-OCT-2011).

CMC, however, did not accept the amount of (b) (4) SLS/capsule (see Type B and C meeting: dated 18-JUL-2013 and 23-OCT-2013), even though the total dose (600 mg) still delivers (b) (4) of SLS. However, CMC made the decision "FDA cannot confirm that the proposed formulation is suitable for registration". While the clinical study was ongoing, CMC advised that the "toxicological assessment provided for (b) (4) sodium lauryl sulfate (SLS) in the formulation of the drug product to be marketed (b) (4) ,,
The application was never put on hold from a CMC perspective.

In a type B meeting on 12-DEC-2013, the Division asked Roche to submit periodic safety update reports to support continuous assessment for potential sodium lauryl sulfate (SLS) related toxicities with alectinib. The sponsor states no known association between SLS and GI perforation. Based on the available data with the dose of 600 mg BID alectinib, the sponsor concludes that the safety profile of the current alectinib formulation remains consistent other ALK inhibitors with regard to GI disorders and they will continue closely monitor these events. The clinical reviewer agrees with the assessment (refer to the Clinical review dated 23-OCT-2014. The Sponsor concludes in their 3rd safety update report shows that based on the available data for the dose of 600 mg BID

alectinib, the safety profile of the current alectinib formulation with regards to GI disorders is consistent with that of other ALK inhibitors not containing SLS. GI disorders will continue to be closely monitored throughout the clinical program, and the next safety update report will be submitted to FDA in October 2015 (refer to the clinical review dated 13-APR-2015).

It appears that the individual ((b) (4) /capsule: total 8 capsules) or total amount (600 mg/day) of SLS does not have safety concern.

There are no novel excipients used in the manufacture of the drug product.

2.3.P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

[redacted]

Chugai Pharmaceutical Co., Ltd. (FEI 3002926698)

The site is responsible for registration stability testing of drug product. The firm has no FDA inspection history in FACTS. A PAI was recommended by OPF/DIA.

The PAI is pending.

Chugai Pharma Manufacturing Co., Ltd. (FEI 3004109596)

The site is responsible for registration stability testing of drug product. The firm has no FDA inspection history in FACTS. A PAI was recommended by OPF/DIA.

The PAI is pending.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

As of 11/5/2015, an Overall Manufacturing Inspection Recommendation for N208434 is pending on the District Office Recommendation for the following facilities:

- ***Chugai Pharmaceutical Co., Ltd. (FEI 3002926698) (pending PAI)***
- ***Chugai Pharma Manufacturing Co., Ltd. (FEI 3004109596) (pending PAI)***

Based on the review of the inspectional history and district file review, all other facilities listed for the NDA (other than the above (2) facilities) are found to be acceptable.

Zhong Li, Ph.D.

Chemist, OPQ/OPF/DIA/IABI

Date: 11/5/2015

Secondary Review Comments and Concurrence:

I concur with the above interim facility review.

Zhihao Peter Qiu, Ph.D.

Branch Chief, OPQ/OPF/DIA/IABI

Date: 11/5/2015

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

36. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

Yes, as a routine quality control tool, the proposed dissolution method is suitable to demonstrate consistency during manufacture and stability testing of the to-be-marketed alectinib capsules.

a. What are the proposed dissolution method parameters?

The proposed dissolution method is summarized in Table 36-1 below.

Table 36-1. Dissolution Method for alectinib 150 mg capsules

Apparatus	USP Apparatus II (Paddle) with spiral coiled sinker
Agitation Speed	100 rpm
Dissolution medium	900 mL simulated gastric fluid without pepsin (SGFsp), pH 1.2, with 4% Triton X-100 (polyoxyethylene [10] octylphenyl ether)
Temperature	37 ± 0.5 °C
Sampling timepoints	30 and 75 min
Sampling	Manual and automatic
Filter	(b) (4)
Quantification of alectinib	high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection at 230 nm.

Source: P.2.P.5.2 Dissolution of Alectinib Drug Product

b. Why were these dissolution method parameters selected?

The optimization of the dissolution process is described as follows.

- Of all the media tested (b) (4) sGFsp (pH 1.2) produced higher solubilization (Table 36-2).
- To achieve sink conditions (b) (4) addition of surfactant was needed. Of all the surfactants tested, only Triton-X effected complete dissolution (Table 36-3). Triton-X concentrations 4% or higher produced (b) (4)% dissolution in (b) (4) minutes, and (b) (4)% dissolution in 75 minutes (Figure 36-1 and Table 36-4).
- Compared with Apparatus (b) (4) with sinkers, the dissolution with Apparatus II (100 rpm) was faster and slightly less variable. (b) (4)

- Using the selected dissolution medium and Apparatus 2 *with sinkers*, 100 rpm as the paddle speed resulted in a plateau of (b) (4)% in 75 min. (b) (4)
- HPLC w/ UV Detection (230 nm) was chosen (b) (4) The HPLC method was successfully validated.
- The dissolution medium volume (900mL) was chosen because it is standard in the USP for immediate release products.
- The sampling timepoints used during development were 5, 10, 15, 20, 30, 45, 60, 75, 90, and 120 minutes which were adequate in characterizing the ascending and the plateau phases of the dissolution curves. Since alectinib is a poorly soluble drug (b) (4) the FDA previously recommended a two-timepoint dissolution specification during the IND phase.

Table 36-2.
Solubility of alectinib hydrochloride in aqueous media across the pH range (pH 1 to 8) at 37 °C

Medium (pH)	Solubility (mg/mL) 1 h/24 h
(b) (4)	

Source: Drug Product Table P-2.2.-4

Table 36-3.
Solubility of alectinib hydrochloride as a function of surfactant

Dissolution Medium Surfactant	pH 1.2	pH 4.0	pH 6.8
(b) (4)			

Source: Drug Product Table P.2.2-5

Figure 36-1
Impact of Triton X-100 level on dissolution profile of alectinib capsules (150 mg) [Batch R2F01]

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

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, **APPROVAL** of NDA 208-434 for Alectinib Tablets, 150 mg, is recommended. The following dissolution method and acceptance criteria have been agreed upon with the Applicant and should be implemented for Alectinib Tablets, 150 mg:

USP Apparatus	Spindle Rotation	Medium/ Volume/Temperature	Acceptance Criteria
2 (Paddle) with spiral coiled sinker	100 rpm	900 ml Simulated Gastric Fluid without pepsin, pH 1.2 with 4 % Triton X-100 (polyoxyethylene[10]octylphenyl ether at 37 ± 0.5 °C	30 min: Q = (b)(4)% 75 min: Q = (b)(4)%

Gerlie Gieser, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/OPQ

10/15/2015

Secondary Review Comments and Concurrence:

I concur with Dr. Gieser's assessment and approval recommendation for NDA 208434, Alectinib Tablets, 150 mg.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/OPQ

10/15/2015

ASSESSMENT OF MICROBIOLOGY

38. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment: SATISFACTORY

Microbiological purity is ensured through manufacturing controls and Drug Product testing. The microbial quality of the Drug Product is controlled by dispensing Drug Substance and excipients that meet the criteria for microbial limits. Further, microbial limits are confirmed by testing at release and on stability

The applicant assessed the stability samples for total aerobic microbial count (TAMC, NMT (b) (4) CFU/g) and total yeasts and molds count (TYMC, NMT (b) (4) CFU/g). Additionally, the absence of *Escherichia coli (E. coli)* for samples at the initial checkpoint was assessed.

Microbiological quality was maintained throughout the study under long-term conditions (25°C/60% RH for 24 months and 30°C/75% RH for 12 months) and accelerated (40°C/75% RH for 6 months) conditions.

2.3.P.7 Container/Closure System

39. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: Not provided

Reviewer's Assessment: N/A

Not applicable for solid oral dosage product

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

40. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: SATISFACTORY

The applicant provided adequate justification and document for (b) (4) milk derived excipient.

The lactose monohydrate is derived from (b) (4) milk. The milk is sourced from healthy animals under the same conditions as milk collected for human consumption. No other ruminant materials (with the exception of (b) (4)) are used in the preparation of lactose.

Hydroxypropyl Methylcellulose Capsule Shell: An animal-free origin was selected to avoid the risk of TSE transmission.

Magnesium Stearate: An animal-free origin has been selected to avoid risks of TSE transmission.

41. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The MICROBIOLOGY section is satisfactory.

Signature: Zhaoyang Meng, Ph.D.
Chemist, OPQ/OPF
11-2-2015

Secondary Review Comments and Concurrence:
I concur with the recommendation of the primary reviewer.

Bogdan Kurtyka
Quality Assessment Lead, OPQ/OPF
11/2/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

42. Is the applicant's claim for categorical exclusion acceptable?

F. Hoffmann-La Roche Inc. claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). The proposed action, approval of an NDA, will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of proposed action.

43. Is the applicant's Environmental Assessment adequate for approval of the application?

The estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of proposed action.

Reviewer's Assessment:

The estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. F. Hoffmann-La Roche Inc. claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant and/or animal material 21 CFR 25.21(b). ***Granted.***

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Rajiv Agarwal
No extraordinary circumstances exist, as referenced in 21 CFR 25.21(a). This drug is manufactured using a synthetic process and is not known to be derived from any wild sourced plant and/or animal material 21 CFR 25.21(b).

Secondary Review Comments and Concurrence: Olen Stephens
I concur that the request for categorical exclusion may be granted
3-Nov-15

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

Roche September 17, 2015 counter proposal

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALECENSA safely and effectively. See full prescribing information for ALECENSA.

ALECENSA® (alectinib) capsules, for oral use
Initial U.S. Approval: XXXX

----------INDICATIONS AND USAGE----------
ALECENSA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, (b) (4) metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

----------DOSAGE AND ADMINISTRATION----------
600 mg orally twice daily. Administer ALECENSA with food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 150 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
(b) (4) Monitor liver laboratory tests (b) (4) every 2 weeks during the first 2 months of treatment, and (b) (4) Withhold, then dose reduce, or permanently discontinue ALECENSA. (2.2, 5.1)

Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 0.4% of patients. Immediately (b) (4) ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified. (2.2, 5.2)

Bradycardia: Monitor heart rate and blood pressure (b) (4) If symptomatic, (b) (4) or permanently discontinue. (2.2, 5.3)

(b) (4)

Embryofetal Toxicity: ALECENSA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.5, 8.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥ 20%) were constipation, edema and myalgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: xx/2015

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	**ALECENSA® (alectinib)**	**Adequate**
Dosage form, route of administration	**Capsules, for oral use**	**Adequate**
Controlled drug substance symbol (if applicable)	Not required	**Adequate**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Capsules: 150 mg	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3 DOSAGE FORMS AND STRENGTHS

150 mg hard capsules, white, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

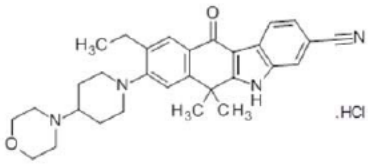
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Capsule	Adequate
Strengths: in metric system	150 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White capsule, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.	Adequate

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

ALECENSA (alectinib) is a (b) (4) kinase inhibitor for oral administration. The molecular formula for alectinib is $C_{30}H_{34}N_4O_2 \cdot HCl$. The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib is described chemically as 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride. The chemical structure of alectinib is shown below:



Alectinib HCl is a white to yellow white powder or powder with lumps with a pKa of 7.05 (base).

ALECENSA is supplied as hard capsules containing 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

Comment [jc41]: To Roche: (b) (4) (b) (4)

Comment [jc42]: To Roche: Remove, (b) (4)

Deleted: (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	**Adequate**
Dosage form and route of administration	Provided	**Adequate**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	**Adequate**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	**Adequate**
Statement of being sterile (if applicable)	Not required	**Adequate**
Pharmacological/ therapeutic class	Provided	**Adequate**
Chemical name, structural formula, molecular weight	Provided	**Adequate**
If radioactive, statement of important nuclear characteristics.	Not required	**Adequate**
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	**Adequate**

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

Hard capsules, white 150 mg capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body, available in:

240 capsules per bottle: NDC 50242-130-01

Storage and Stability: Do not store above 30°C (86°F). Store in the original container to protect from light and moisture.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	150 mg	**Adequate**
Available units (e.g., bottles of 100 tablets)	240 capsules	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	**Adequate**
Special handling (e.g., protect from light, do not freeze)	Provided	**Adequate**
Storage conditions	Provided	**Adequate**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: **Genentech USA, Inc.** A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	**Adequate**

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	**ALECENSA™** (alectinib)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	150 mg Equivalency statement is also provided (Each capsule contains 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl)	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	240 Capules	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for an oral dosage form	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Warnings	Protect from light and moisture	Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Carton Labeling

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	**ALECENSA™** (alectinib)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	150 mg Equivalency statement is also provided (Each capsule contains 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl)	Adequate
Net contents (21 CFR 201.51(a))	240 capsules	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not required for an oral dosage form	Adequate
Sterility Information (if applicable)	Space is provided	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of children" (optional for Rx,	Protect from light and moisture	Adequate

required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	Adequate

Conclusion: Adequate

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Rajiv Agarwal
Revisions to the proposed PI labeling (Highlight, Description and How Supplied sections) have been conveyed to the OND PM and will be finalized during team review of the labeling.

Secondary Review Comments and Concurrence: Olen Stephens
Labeling discussions are on-going through the clinical division.

II. List of Deficiencies To Be Communicated

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters •Scale/equipments • Site	L	Factors identified in CQA will not affect the assay or stability	Acceptable	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC
Physical stability (solid state)	• Formulation • Raw materials • Process parameters •Scale/equipments • Site	M	Factors identified in CQA will not affect the physical stability	Acceptable	No comment
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Adequate weight Variation assay	Acceptable	(b) (4) Changes in formulation or process should be assessed according to relevant SUPAC

Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during development	Acceptable	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.
Dissolution – BCS Class IV	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during development	Acceptable	Changes in formulation or process should be assessed according to relevant SUPAC Guidances for Post-Approval changes.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208434	**Submission Type: 505(b)(1)**	**Established/Proper Name: Alectinib**
Applicant: Hoffman-La Roche Inc.	**Letter Date: July 6, , 2015**	**Dosage Form: Oral Capsule**
Chemical Type: 1 (small molecule)	**Stamp Date: July 6, , 2015**	**Strength: 150mg**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Not at this time.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	
17.	Biosimiliar product[1]	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
18.	Combination Product		☐	☒	
19.	Other		☐	☒	
	Regulatory Considerations				
20.	USAN Name Assigned		☒	☐	
21.	End of Phase II/Pre-NDA Agreements		☒	☐	June 23, 2013 BT designation July 22, 2013 EOP1 meeting October 23, 2013 Type C CMC Meeting March 18, 2014 EOP2 CMC meeting November 17, 2014 Pre-NDA meeting SLS issues March 19, 2015 Pre-NDA (b)(4)% SLS fileability issues April 7, 2015 clinical pre-NDA meeting for any issues to support the NDA
22.	SPOTS (Special Products On-line Tracking System)		☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒	
24.	Comparability Protocol(s)[2]		☐	☒	None identified in the filing reivew
25.	Other_____		☐	☐	
	Quality Considerations				
26.	Drug Substance Overage		X	☒	
27.	Design Space	Formulation	☐	☒	
28.		Process	☐	☒	
29.		Analytical Methods	X		proposed risk management approaches are included . In my view , it was not part of an overall QbD approach.
30.		Other	☐	☒	
31.	Real Time Release Testing (RTRT)		☐	☒	
32.	Parametric Release in lieu of Sterility Testing		☐	☒	
33.	Alternative Microbiological Test Methods		☐	☒	
34.	Process Analytical Technology[1]		☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐	
36.		Excipients	☒	☐	None of the excipients are of animal or human origin
37.		Microbial	☒	☐	
38.	Unique analytical methodology[1]		☐	☒	
39.	Excipients of Human or Animal Origin		☒	☐	
40.	Novel Excipients		☐	☒	(b) (4) SLS used and the high quality standard for acceptance criteria needs to be considered rather than just based on NF grade.
41.	Nanomaterials[1]		☐	☒	
42.	Hold Times Exceeding 30 Days		☐	☒	
43.	Genotoxic Impurities or Structural Alerts		☒	☐	
44.	Continuous Manufacturing		☐	☒	
45.	Other unique manufacturing process[1]		☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒	
47.	New delivery system or dosage form[1]		☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
48.	Novel BE study designs	☐	☒	
49.	New product design[1]	☐	☒	
50.	Other_____	☐	X	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? 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? 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)	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☐	☐	☒	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system ❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☒	☐	☐	Use of validation DS batch from the proposed comparability protocol
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient	☒	☐	☐	

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	information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION				
	BIOPHARMACEUTICS				

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C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	Per revised MOU, *in vivo* BA/BE studies in submissions are OCP's review responsibility.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☐	☒	The to-be-marketed 150 mg oral capsule containing (b)(4)% SLS was evaluated in the two pivotal clinical trials NP28761 and NP28673. Study NP28761 compared the PK of the 150 mg capsule (proposed for marketing in the US) to the 20 mg and 40 mg capsules (also with (b)(4)% SLS) marketed in Japan, and used in the first-in-human study (Study AF-001JP). (b) (4) [redacted]
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	The proposed product is an immediate release capsule.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☒	☐	Alectinib has low solubility in aqueous buffers across the pH range. Absolute bioavailability is low (37%).
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation,	☐	☐	☒	

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	sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			X	

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1A: Product Design FMEA - Solid Oral Products

			Non-High Risk Drugs				High Risk Drugs			
PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	(b) (4)	Highly stable drug (1)	2	Release (1)	2	Highly stable drug (1)	4	Release (1)	4
					Stability (3)	6			Stability (3)	12
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site			(b) (4)	4	8		(b) (4)	4	36
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		(b) (4)	3	4	24	(b) (4)	4	4	32

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1A: Product Design FMEA - Solid Oral Products

			Non-High Risk Drugs				High Risk Drugs			
PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	(b) (4)	1	2	Release with spec (3)	6	1	2	Release with spec (3)	6
Dissolution – BCS Class (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		3	2	2	12	3	4	2	24

Olen Stephens -S

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