CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202192, JAKAFI (ruxolitinib) Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg
Date: 21-OCT-2011

Introduction

JAKAFI (ruxolitinib) tablets are indicated for the treatment of myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

JAKAFI (ruxolitinib) Tablets may be administered with or without food. As necessary, JAKAFI tablets can be administered through a nasogastric tube. Doses are titrated based on safety and efficacy. The maximum dose is 25 mg twice daily.

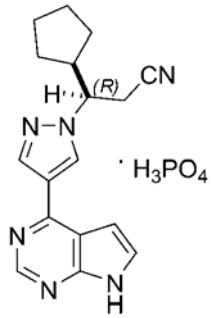
Adminstrative

Supported by IND 77,456 and five DMFs, this original 505(b)(1) NDA was received 03-JUN-2011 from Incyte Corporation of Wilmington, DE and was given Priority review status.

A total of 12 amendments received between 10-JUN-2011 and 19-OCT-2011 were also reviewed. This was a team review within ONDQA. An EES finding of "overall acceptable" is dated11-OCT-2011. The ONDQA Biopharm review was entered into DARRTS on 20-OCT-2011.

ONDQA recommends approval from the CMC perspective.

Drug Substance: ruxolitinib phosphate

Chemical structure	
Molecular formula	$C_{17}H_{21}N_6O_4P$
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]:free base; [1092939-17-7]: phosphate salt

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer. (b) (4) (b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

Drug Product: JAKAFI Tablets 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

JAKAFI Tablets are provided in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths. The tablets contain **ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base**.

The drug product also contains the following inactive ingredients: microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxylpropyl cellulose. (b) (4) (b) (4)

All the five strengths of ruxolitinib tablets (b) (4) (b) (4) Jakafi™ (ruxolitinib) Tablets are immediate release, non-coated tablets. They are white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either "5", or "10", or "15", or "20", or "25" while other side remaining the same as "INCY". JAKAFI Tablets are supplied in 75 mL HDPE bottles of 60 tablets.

CONVEY THE COMMENT BELOW TO APPLICANT IN ACTION LETTER:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

Thank you.

Rik Lostritto, Ph.D., Director, ONDQA Division I.

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/s/

RICHARD T LOSTRITTO
10/21/2011

NDA 202192

Jakafi™ (ruxolitinib) Tablets

Incyte Corporation

Drug Product Section of Team Review

Joyce Crich, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
For the Division of Hematology Products

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CMC Review Data Sheet

1. NDA 202192

2. REVIEW #: 1

3. REVIEW DATE: 20-Oct-2011

4. REVIEWER: Joyce Crich, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 77,456 submission	30-Mar-2007
IND 77,456 CMC review of amendment (SDN# 93)	02-Oct-2009
IND 77,456 CMC review of amendment (SDN# 172)	04-Feb-2011
CMC end-of-phase-2 meeting (03-Dec-2008) minutes	02-Jan-2009
Type C CMC-only meeting (08-Jul-2009) minutes	02-Oct-2009
CMC only pre-NDA meeting (30-Nov-2010) minutes	20-Dec-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03-Jun-2011	03-Jun-2011
Request for proprietary name (Jakafi) review	2	10-Jun-2011	10-Jun-2011
Response to FDA 29-Jun-2011 IR regarding dissolution data and nasogastric administration	3	08-Jul-2011	08-Jul-2011
Response to FDA 27-Jul-2011 IR regarding comparability protocols)	5	01Aug-2011	01Aug-2011
Background information for proprietary name)	6	04-Aug-2011	04-Aug-2011
Container and carton labeling	7	05-Aug-2011	05-Aug-2011
Container and carton labeling	9	18-Aug-2011	18-Aug-2011
Updated container and carton labeling	11	29-Aug-2011	29-Aug-2011
Stability update for drug substance and drub product	12	30-Aug-2011	30-Aug-2011
Withdrawal of two comparability protocols	13	12-Sep-2011	12-Sep-2011
Response to 16-Sep-2011 CMC IR	15	27-Sep-2011	27-Sep-2011
Response to 04-Oct-2011 CMC IR	19	12-Oct-2011	12-Oct-2011
Response to 18-Oct-2011 Telecon	20	19-Oct-2011	19-Oct-2011

Reference ID: 3032104

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Incyte Corporation
Address:	Route 141 & Henry Clay Road Building 336 Wilmington, DE 19880
Representative:	Ronald C Falcone, Ph.D., Vice President, Regulatory Affairs
Telephone:	302-498-6846

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Jakafi™
b) Non-Proprietary Name: ruxolitinib tablets
c) Code Name/# (ONDQA only): INCB018424 (free base), INCB018424 phosphate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1 (new molecular entity)
- Submission Priority: P (priority review)

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

10. PHARMACOL. CATEGORY: antineoplastic agent (a kinase inhibitor for Janus Associated Kinases (JAKs) JAK1 and JAK2)

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

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

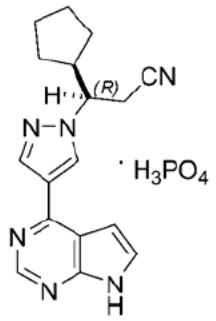
_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

Reference ID: 3032104

CMC Review Data Sheet

Chemical structure	
Molecular formula	$C_{17}H_{21}N_6O_4P$
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]:free base; [1092939-17-7]: phosphate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			3	Adequate	06-Dec-2008	Reviewed by Gene Holbert

[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
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)

Reference ID: 3032104

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	77,456	INCB018424 (ruxolitinib phosphate)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Oct-2011	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable*	See DARRTS for review*	Wei Chen
Biopharm	Acceptable	20-Oct-2011	Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending**		
DMEPA	The proposed proprietary name, Jakafi, is acceptable	16-Sep-2011	Lissa Owens
EA	Categorical exclusion (see review)	11-Oct-2011	Joyce Crich
Microbiology	Approval from microbiology product quality standpoint	23-Aug-2011	John W. Metcalfe

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewers in her 9/8/11 and 9/16/11 e-mails that the acceptance criteria for the impurities in the drug substance are qualified. None of the impurities are considered genotoxic, based on the submitted toxicology data. See Section III of the drug substance review for the e-mail correspondences.

**Methods validation consult was sent to the FDA St. Louis Laboratory on 08-Sep-2011. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

Reference ID: 3032104

The CMC Review for NDA 202192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Include the following language in the approval letter:
Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is ruxolitinib phosphate, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer. (b) (4)

Detailed information regarding designation of the proposed starting materials for (b) (4) their commercial sources, acceptance criteria, and associated methods of analysis are provided in Section 3.2.S.2.3.1. The fate of starting materials and their impurities, data from purging studies, and change control

Reference ID: 3032104

strategies for the manufacturing changes for starting materials are provided in the 27-Sep-2011 amendment, in response to the FDA 16-Sep-2011 request. The results from purging studies demonstrate that the manufacturing process is capable of removing the impurities to the desired levels.

Ruxolitinib phosphate is a white to off-white to light pink powder. It has been classified as a BCS Class 1 compound (highly soluble and highly permeable material). It is non-hygroscopic. Polymorph screening has been carried out and only [redacted] (b) (4)

The submitted stability data support the proposed retest period of [redacted] (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Jakafi™(ruxolitinib) Tablets are available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg dosage strengths. The tablets contain ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxyl propyl cellulose. All the five strengths of ruxolitinib tablets [redacted] (b) (4) [redacted] (b) (4) [redacted]

Jakafi™(ruxolitinib) Tablets are immediate release, uncoated tablets, white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either number "5", or "10", or "15", or "20", or "25" while other side remaining the same as "INCY". Jakafi™(ruxolitinib) Tablets are supplied in 75 ml HDPE bottles of 60 tablets.

Formulation development of ruxolitinib tablets was performed by Incyte through three sites; [redacted] (b) (4) and DSM. The basic steps in the manufacturing process [redacted] (b) (4) Standard release specifications for solid oral dosage forms have been proposed. DSM Pharmaceuticals, Inc. is the proposed commercial site for the drug product manufacturing, release testing, packaging, labeling and stability study.

The applicant submitted the stability data from three primary batches for the5 mg strength and 25 mg strength tablets up to 18 months at 25°C/60% RH and up to 6

Reference ID: 3032104

months at 40°C/75% RH, and the additional stability data from eleven supportive batches across the five different strengths. Those stability data support the proposed 24 months shelf-life for the drug product in all five strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary and supportive lots indicate that the drug product does not require protection from light.

The provided nasogatric (NG) tube study results confirm the compatibility between the drug product and NG tubes (≥ 8 French, three type tubes from Kendall) as well as the suspension stability of the tablets in water for up to 6 hours. The data demonstrate that it is suitable for administration of drug in aqueous suspension through a nasogastric tube to patients who have difficulty swallowing.

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

Jakafi™(ruxolitinib) Tablets are indicated for treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocy-themia myelofibrosis.

Jakafi™(ruxolitinib) Tablets are dosed orally and can be administered with or without food. For patients unable to ingest tablets, Jakafi™(ruxolitinib) Tablets can be administered through a nasogastric tube (≥ 8 French) as follows: (1) Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes; (2) Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube using an appropriate syringe. The tube should be rinsed with additional water.

The recommended starting dose of Jakafi™(ruxolitinib) Tablets is 15 mg given orally twice daily for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L and 20 mg twice daily for patients with a platelet count of > 200 X 10^9/L. There is limited information to recommend a starting dose for patients with platelet counts between 50 X 10^9/L and 100 X 10^9/L. The recommended starting dose in these patients is 5 mg twice daily.

Doses may be titrated based on safety and efficacy. The maximum dose of Jakafi™ (ruxolitinib) Tablets is 25 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Jakafi.

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Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 12-Oct-2011 are acceptable from the CMC perspective.

The Office of Compliance has issued an overall "acceptable" recommendation dated 11-Oct-2011 for all facilities used for manufacturing and control of the drug substance and drug product.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Joyce Crich, Ph.D, Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Janice Brown, Ph.D., CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DFS

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/s/

JOYCE Z CRICH
10/20/2011

JANICE T BROWN
10/20/2011
Janice Brown for Sarah Pope Miksinski, Ph.D.

NDA 202192

Jakafi™ (ruxolitinib) Tablets

Incyte Corporation

Review of Drug Substance Sections

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Hematology Products

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Reference ID: 3031960

CMC Review Data Sheet

1. NDA 202192

2. REVIEW #: 1

3. REVIEW DATE: 20-Oct-2011

4. REVIEWER: Sue-Ching Lin, M.S., R.Ph. (Drug Substance Sections)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 77,456 submission	30-Mar-2007
IND 77,456 CMC review of amendment (SDN# 93)	02-Oct-2009
IND 77,456 CMC review of amendment (SDN# 172)	04-Feb-2011
CMC end-of-phase-2 meeting (03-Dec-2008) minutes	02-Jan-2009
Type C CMC-only meeting (08-Jul-2009) minutes	02-Oct-2009
CMC only pre-NDA meeting (30-Nov-2010) minutes	20-Dec-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03-Jun-2011	03-Jun-2011
Request for proprietary name (Jakafi) review	2	10-Jun-2011	10-Jun-2011
Response to FDA 29-Jun-2011 IR regarding dissolution data and nasogastric administration	3	08-Jul-2011	08-Jul-2011
Response to FDA 27-Jul-2011 IR regarding comparability protocols)	5	01Aug-2011	01Aug-2011
Background information for proprietary name)	6	04-Aug-2011	04-Aug-2011
Container and carton labeling	7	05-Aug-2011	05-Aug-2011
Container and carton labeling	9	18-Aug-2011	18-Aug-2011
Updated container and carton labeling	11	29-Aug-2011	29-Aug-2011
Stability update for drug substance and drub product	12	30-Aug-2011	30-Aug-2011
Withdrawal of two comparability protocols	13	12-Sep-2011	12-Sep-2011
Response to 16-Sep-2011 CMC IR	15	27-Sep-2011	27-Sep-2011
Response to 04-Oct-2011 CMC IR	19	12-Oct-2011	12-Oct-2011
Response to 18-Oct-2011 telecon	20	19-Oct-2011	19-Oct-2011

Reference ID: 3031960

7. NAME & ADDRESS OF APPLICANT:

Name:	Incyte Corporation
Address:	Route 141 & Henry Clay Road Building 336 Wilmington, DE 19880
Representative:	Ronald C Falcone, Ph.D., Vice President, Regulatory Affairs
Telephone:	302-498-6846

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Jakafi™
b) Non-Proprietary Name: ruxolitinib tablets
c) Code Name/# (ONDQA only): INCB018424 (free base), INCB018424 phosphate (drug substance)
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1 (new molecular entity)
- Submission Priority: P (priority review)

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

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

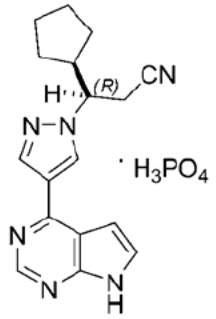
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

Reference ID: 3031960

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

Chemical structure	
Molecular formula	$C_{17}H_{21}N_6O_4P$
Molecular weight	404.36 g/mole
United States Adopted Name (USAN)	ruxolitinib phosphate
Chemical name	(*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate
Chemical Abstracts Service (CAS) registry number	[941678-49-5]:free base; [1092939-17-7]: phosphate salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			4			See section 3.2.P.7
	III			3	Adequate	06-Dec-2008	Reviewed by Gene Holbert

[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
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	77,456	INCB018424 (ruxolitinib phosphate)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Oct-2011	D. Smith
Pharm/Tox	Impurity limits in drug substance are acceptable*	See DARRTS for review*	Wei Chen
Biopharm	Acceptable	20-Oct-2011	Tien-Mien Chen
LNC	N/A		
Methods Validation	Pending**		
DMEPA	The proposed proprietary name, Jakafi, is acceptable	06-Sep-2011	Lissa Owens
EA	Categorical exclusion	Date of this review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint	23-Aug-2011	John W. Metcalfe

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewers in her 9/8/11 and 9/16/11 e-mails that the acceptance criteria for the impurities in the drug substance are qualified. None of the impurities are considered genotoxic, based on the submitted toxicology data. See Section III of the drug substance review for the e-mail correspondences.

**Methods validation consult was sent to the FDA St. Louis Laboratory on 08-Sep-2011. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

Reference ID: 3031960

The CMC Review for NDA 202192

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg) when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF).

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The drug substance is ruxolitinib phosphate, which is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA.

Ruxolitinib phosphate is chemically synthesized as a *R*-isomer [redacted] (b) (4)

Detailed information regarding designation of the proposed starting materials for [redacted] (b) (4) their commercial sources, acceptance criteria, and associated methods of analysis are provided in Section 3.2.S.2.3.1. The fate of starting materials and their impurities, data from purging studies, and change control strategies for the manufacturing changes for starting materials are provided in the

Reference ID: 3031960

27-Sep-2011 amendment, in response to the FDA 16-Sep-2011 request. The results from purging studies demonstrate that the manufacturing process is capable of removing the impurities to the desired levels.

Ruxolitinib phosphate is a white to off-white to light pink powder. It has been classified as a BCS Class 1 compound (highly soluble and highly permeable material). It is non-hygroscopic. Polymorph screening has been carried out and only [redacted] (b) (4)

The submitted stability data support the proposed retest period of [redacted] (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

(2) Drug Product

Jakafi™(ruxolitinib) Tablets are available in 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg dosage strengths. The tablets contain ruxolitinib phosphate as the active pharmaceutical ingredient equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base. The drug product also contains the following inactive ingredients: microcrystalline cellulose, lactose, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxylpropyl cellulose. All the five strengths of ruxolitinib tablets are [redacted] (b) (4) (b) (4)

Jakafi™ (ruxolitinib) Tablets are immediate release, uncoated tablets, white to off-white in color in different sizes and shapes (round for 5 mg and 10 mg strength, oval for 15 mg strength, capsule-shaped for 20 mg strength, and oval for 25 mg strength), with debossing on one side of tablets to reflect the strength with either number "5", or "10", or "15", or "20", or "25" while other side remaining the same as "INCY". Jakafi™ (ruxolitinib) Tablets are supplied in 75 mL HDPE bottles of 60 tablets.

Formulation development of ruxolitinib tablets was performed by Incyte through three sites: [redacted] (b) (4) DSM. The basic steps in the manufacturing process [redacted] (b) (4) Standard release specifications for oral solid dosage forms have been proposed. DSM Pharmaceuticals, Inc. is the proposed commercial site for the drug product manufacturing, release testing, packaging, labeling and stability study.

The applicant submitted the stability data from three primary batches for the5 mg strength and 25 mg strength tablets up to 18 months at 25°C/60% RH and up to 6 months at 40°C/75% RH, and the additional stability data from eleven supportive batches across the five different strengths. Those stability data support the proposed

24 months shelf-life for the drug product in all five strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary and supportive lots indicate that the drug product does not require protection from light.

The provided nasogatric (NG) tube study results confirm the compatibility between the drug product and NG tubes as well as the suspension stability of the tablets in water for up to 6 hours. The data demonstrate that it is suitable for administration of the drug in aqueous suspension through a nasogastric tube to patients with difficulty swallowing.

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

The drug product is indicated for treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Jakafi™(ruxolitinib) Tablets are dosed orally and can be administered with or without food. For patients unable to ingest tablets, Jakafi™(ruxolitinib) tablets can be administered through a nasogastric tube (≥ 8 French) as follows: (1) Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes; (2) Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube using an appropriate syringe. The tube should be rinsed with additional water.

The recommended starting dose of Jakafi™(ruxolitinib) Tablets is 15 mg given orally twice daily for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L and 20 mg twice daily for patients with a platelet count of > 200 X 10^9/L. There is limited information to recommend a starting dose for patients with platelet counts between 50 X 10^9/L and 100 X 10^9/L. The recommended starting dose in these patients is 5 mg twice daily.

Doses may be titrated based on safety and efficacy. The maximum dose is 25 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Jakafi.

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 12-Oct-2011 are acceptable from the CMC perspective.

The Office of Compliance has issued an overall "acceptable" recommendation dated 11-Oct-2011 for all facilities used for manufacturing and control of the drug substance and drug product.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Janice Brown, CMC Lead, Division of New Drug Quality Assessment I, Office of New Drug Quality Assessment (ONDQA)

Sarah Pope Miksinski, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

SUE CHING LIN
10/20/2011

JANICE T BROWN
10/20/2011
Janice Brown for Sarah Pope Miksinski, Ph.D.

Initial Quality Assessment
Division of New Drug Quality Assessment I
Branch II

OND Division:	Division of Hematology Products
NDA:	202192
Applicant:	Incyte Corporation
Stamp Date:	03-Jun-2011
PDUFA Date:	03-Dec-2011
Proprietary (Brand) Name of Drug Product:	Jakavi
Established Name:	Ruxolitinib phosphate tablets
Dosage Form(s):	Immediate release tablets
Strength(s):	5 mg, 10 mg, 15 mg, 20 mg, and 25 mg
Route of Administration:	Oral
Proposed Indication(s):	Treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis
CMC Lead:	Janice Brown, Branch II/DNDQA1/ONDQA
Chief, Branch II:	Sarah Pope Miksinski, Ph.D., DNDQA1/ONDQA

Review team recommendation: Team review

	Yes	No	
ONDQA Fileability:	X	☐	
Comments for 74-Day Letter	X	☐	(see page 10)

CONSULTS/ CMC RELATED REVIEWS

Consult	**Comment**
Biopharm	Assigned to Kareen Riviere, Ph.D. to evaluate both biowaiver requests
CDRH	Not Applicable
EA	Categorical Exclusion requested
EES	Inspection request was submitted on 09-Jun-2011
DMEPA	Labeling consult request will be sent as part of DHP request.
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.
Microbiology	Microbiology consult was requested on 06-Jun-2011
Pharm-Tox	Determined by primary reviewer

SUMMARY

Ruxolitinib tablets (INCB018424 and INC424) is a new molecular entity indicated for the treatment of patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera- Myelofibrosis (PPV-MF), or Post-Essential Thrombocythemia Myelofibrosis (PET-MF). Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Ruxolitinib is supplied as 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets. The recommended starting dose of ruxolitinib is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/μL and 20 mg twice daily for patients with an initial platelet count of > 200,000/μL. The highest human therapeutic dose is 25 mg bid orally.

STARTING MATERIALS

1. Agreement on the starting material classificatio [redacted] (b) (4) was reached between the FDA and Incyte during a pre-NDA meeting held on 30-Nov-2010.

DRUG SUBSTANCE

2. Ruxolitinib phosphate is small molecule drug manufacture [redacted] (b) (4)

3. A complete list of manufacturing facilities is appended as attachment 1.

4. Ruxolitinib phosphate has a chiral center at C-3. The asymmetric carbon possesses an (*R*) – configuration. The polymorph screening of ruxolitinib phosphate showed [redacted] (b) (4) The chiral testing data showed that the major impurity, [redacted] (b) (4) remained unchanged throughout the stability studies.

5. **IMPURITIES**

Reference ID: 2972073

5.1 The applicant has identified twelve product related impurities that may arise during the synthesis and purification of ruxolitinib phosphate. Reproduced in table 1 below is a summary of the impurities and the levels found in batches. Adequacy of the proposed limits will be determined by the reviewer.

(b) (4)

5.2 **Genotoxicity** - *In silico* analysis was used to screen identified and potential impurities, starting materials and intermediates for mutagenicity. (b) (4) None were found to be genotoxic. The remaining impurities that were analyzed by the program did not identify any structural alerts and were not tested any further.

Reference ID: 2972073

5.3 Heavy Metals – The applicant includes the Heavy Metals by USP <231> limit test for heavy metals in the drug substance but does not identify the type of heavy metal that may be present in the drug substance. USP <231> is a qualitative test that demonstrates that the content of metallic impurities below a specified limit. Substances that typically respond to this test are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum. All drug substance batches contained (b) (4) of Heavy Metals. The level of residual heavy metals is controlled in the drug substance specification with a limit of (b) (4)

5.4 Palladium (Pd) Content - (b) (4)

5.5 Residual Organic Solvents - (b) (4) Limits for each residual organic solvent in the final drug substance were established based on ICH Q3C guidance. No batches exceed the established limit.

6.0 DRUG SUBSTANCE SPECIFICATION - The ruxolitinib phosphate drug substance specification is appended as attachment 4.

7.0 CONTAINER – CLOSURE - The primary container for the drug substance (b) (4)

8.0 STABILITY – The applicant submitted long-term and accelerated stability studies on ruxolitinib phosphate batches manufactured by (b) (4) (Lots 08-340-001R, 09-340-003 and 09-340-004) (b) (4) (Lots 08-340-002, 11-340-011 and 11-340-012). At the request of the Division (Information Request, dated December 22, 2010), two additional batches of drug substance manufactured (b) (4) and added to the stability studies.

8.1. Description, identification, assay, related substances, chirality and water content are monitored in the stability program.

8.2 The drug substance is surprisingly stable. Stability data showed that the drug substance primary stability batches have remained essentially unchanged; no degradation products are detected above the ICH reporting threshold of 0.05%.

8.3 The chiral testing data showed that the major impurity (b) (4) (b) (4) remained unchanged during storage at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH.

8.2 The applicant is requesting a re-test period of (b) (4) when stored at 25°C/60% RH. As additional data becomes available, the retest date may be extended.

Reference ID: 2972073

8.3 Photostability study results show that ruxolitinib phosphate drug substance manufactured by [redacted] (b) (4) is not photosensitive.

DRUG PRODUCT

9.0 Ruxolitinib phosphate drug product is formulated as an immediate release tablet for oral administration. The ruxolitinib phosphate tablets 5 mg, 10 mg, 15 mg, 20 mg and 25 mg [redacted] (b) (4)

10.0 The BCS committee reviewed the solubility, permeability, and dissolution information provided and concluded that INCB018424 phosphate is a BCS Class 1 compound (see correspondence dated 7/20/2009). The applicant requested a biowaiver for bioequivalence requirement for the 10 mg, 15 mg, 20 mg and 25 mg strength tablets. ONDQA Biopharmacology group will review the biowaiver request.

11.0. The tablet composition is summarized in table 2 below.

Table 2: Composition of Ruxolitinib Phosphate Tablets

Component	Quality Standard	Amount (mg/tablet)					Function
		5 mg	10 mg	15 mg	20 mg	25 mg	
Ruxolitinib Phosphate[a]	Incyte specification	[redacted] (b) (4)					
Microcrystalline Cellulose	NF/EP/JP						
Lactose Monohydrate	NF/EP/JP						
Colloidal Silicon Dioxide	NF/EP						
Hydroxypropyl Cellulose	NF/EP						
Povidone	USP/EP						
Sodium Starch Glycolate	NF/EP						
Magnesium Stearate	NF/EP/JP						
[redacted] (b) (4)	USP/EP						
Total Tablet Weight (mg)	-						

[redacted] (b) (4)

12. All excipients (microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, hydroxypropyl cellulose, povidone, sodium starch glycolate, and magnesium stearate) used in the manufacturing of ruxolitinib phosphate tablets meet the current USP/NF specifications. Lactose monohydrate, NF in the tablet formulation is of animal origin. Verify that that

Reference ID: 2972073

animal sourced lactose monohydrates complies with http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=9&PART=94&SECTION=18&TYPE=TEXT . The bovine milk derivatives used in the manufacture of the lactose originate from the U.S. Magnesium stearate, NF used in the tablet formulation is of vegetable origin.

13. The manufacturing flow diagram is reproduced in attachment 5. The drug product is manufactured using (b) (4)

14. The drug product specification for all strengths is listed in table 3.

Table 3: Drug Product Specification (all strengths)

Test		Acceptance Criteria	Method
Description	5 mg	White to off-white round tablets debossed with INCY on one side and 5 on the other side	IC/000000/030
	10 mg	White to off-white round tablets debossed with INCY on one side and 10 on the other side	
	15 mg	White to off-white oval tablets debossed with INCY on one side and 15 on the other side	
	20 mg	White to off-white capsule shaped tablets debossed with INCY on one side and 20 on the other side	
	25 mg	White to off-white oval tablets debossed with INCY on one side and 20 on the other side	
Identification HPLC Retention Time		The retention time of the principal peak in the sample chromatogram corresponds to that in the standard chromatogram.	IC/018424/011
UV Absorption		The UV absorption spectra of the test solution and the standard solution exhibit maxima and minima at the same wavelengths.	USP <197U>
Assay (w/w %)		(b) (4) of label claim	IC/018424/011
Degradation Products (Area %) Unspecified (Individual)		(b) (4)	IC/018424/011
Total		(b) (4)	
Content Uniformity		Conforms to USP <905> requirement for uncoated tablets	IC/018424/011
Dissolution		(b) (4) (Q) of the Label Claim dissolved in 30 min as defined in USP <711>	IC/018424/027
(b) (4)		(b) (4)	(b) (4)

Reference ID: 2972073

14.1 Since the tablets of five strengths consistently meet compendial microbial limits, the applicant proposes to omit microbial limit testing in drug product release and stability testing. A microbiology consult was requested to evaluate appropriateness of removing routine microbial testing.

14.2 Ruxolitinib phosphate drug product exhibits rapid dissolution profiles (b) (4) dissolved in 15 min) in 0.1 N HCl, pH 4.5 and pH 6.8 buffers.

15.0 **Closure System –** All strengths of ruxolitinib phosphate drug product tablets are packaged in a 60-count presentation in 75 cc, HDPE bottles. The bottles are capped with (b) (4)

16.0 **Drug Product Stability Studies**

16.1 During a pre-NDA meeting, the agency requested that two additional batches of drug substance produced using (b) (4) to confirm the equivalency between the ruxolitinib phosphate batches obtained either from (b) (4) Two batches of 5 mg tablets and two batches of 25 mg tablets (one batch of each strength from Lots 11-340-011 and from 11-340-012) have been manufactured. The stability data (three-month accelerated and long term) of the two batches of 5 mg tablets (Lots A76072 and A76073) and two batches 25 mg tablets (Lots A76074 and A76075) will be submitted in a stability update during the NDA review cycle.

16.2 The applicant used a (b) (4)

16.3 The drug product quality attributes, description, identification, assay, degradation products, and (b) (4) were monitored in the stability program.

16.4 Stability results of 5 mg and 25 mg ruxolitinib phosphate tablets show that no degradation products are observed above the ICH reporting threshold (0.1%) during storage at long term conditions (25°C/60% RH) for at least 18 months and accelerated conditions (40°C/75% RH) for up to 6 months.

16.5 Chirality - Since release testing and stability study data of the 5 mg and 25 mg tablets demonstrate that no racemization is observed during drug product manufacture or storage, chiral stability will not be monitored on future drug product tablet stability batches. The chiral stability has been confirmed during long-term and accelerated storage conditions on both drug substance and drug product tablets.

Reference ID: 2972073

16.6 The applicant is requesting a shelf life of 24 months for ruxolitinib phosphate tablets of the five strengths under the long term storage conditions at 25 ± 2°C/60 ± 5% RH.

16.7 Based on the results of the photostability study, ruxolitinib phosphate tablets are not light sensitive.

16.8 Nasogastric (NG) Tube Study Procedure – For patients that can't swallow tablets, the applicant evaluated the stability of the crushed tablet suspended in sterile purified water and held for 6 hours at room temperature. They followed the same bracketing strategy where they used 5 mg and 25 mg tablets along with three types of NG tubes. Samples were analyzed for assay and degradation products. Little to no degradation was observed in NG Tube Compatibility samples as compared to control samples.

The applicant requested a biowaiver to establish the in vivo bioequivalence between the disperse solution/suspension product and the intact tablets of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. The biowaiver will be reviewed by ONDQA Biopharm group.

17. COMPARABILITY PROTOCOL – Two comparability protocols were included the submission.

17.1 Additional Drug Product Manufacturer - Incyte intends to qualify additional drug product manufacturers for the manufacture, release testing, packaging, labeling and stability study for ruxolitinib phosphate tablets of 5 mg, 10 mg, 15 mg, 20 mg and 25 mg strengths; however, the manufacturing site has not been determined. As noted in the 2003 Draft Guidance for Comparability Protocol, the new manufacturing site must have a satisfactory CGMP inspection. There are a number of issues that have been identified and sent to the applicant (see comments to the applicant in 74 day letter).

17.2 Additional Drug Substance Manufacturer - Incyte plans to qualify alternate suppliers for ruxolitinib phosphate for future commercial production (b) (4) (b) (4) As with the alternate drug product manufacturer, Incyte has not determined the new drug substance manufacturer. See comments in 74-day letter.

18. DMF - The following DMFs were referenced. Review recommendations are included in the comments column.

Reference ID: 2972073

Supporting DMFs:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	III		(b) (4)	No chemistry review is needed The item referenced was found adequate for tablets on 06-Dec-04. This review was located using http://fdaesearch.fda.gov/
	III			No chemistry review is needed The HDPE bottle referenced was found adequate for tablets on 15-Sep-2000. This review was located using http://fdaesearch.fda.gov/
	III			A review is needed
	III			No chemistry review is needed The item referenced was found adequate for solid oral dosage packaging on 06-Dec-2004. This review was located using http://fdaesearch.fda.gov/
	III			A chemistry review is needed

17. Adventitious Agents – As noted in #12, lactose monohydrate, NF in the tablet formulation is of animal origin. Verify that the animal sourced lactose monohydrate complies with http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=9&PART=94&SECTION=18&TYPE=TEXT .

18. Environmental Assessment: The applicant has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

19. Establishment Evaluation*:* A full list of facilities involved in the manufacture, packaging and testing of ruxolitinib phosphate tablets is reproduced in attachment 1.

CRITICAL ISSUES FOR REVIEW

1. Overall, this NDA is well written and the conclusions are supported by actual data.

Reference ID: 2972073

2. Based on the batch data, the applicant is requesting removal of microbial limits and chirality testing in the drug product stability protocol. Microbiology will review removal of the microbial testing. Removal of chiral testing should be assessed by the CMC reviewer.

3. Generally particle size distribution is a critical to dissolution properties. Batch data indicate that the particle size distribution is relatively consistent. In this case due to the high aqueous solubility, the particle size distribution of ruxolitinib phosphate is not likely to have a significant impact on drug product dissolution.

4. See comments for Comparability Protocol in 74-day letter.

Comments for 74-Day Letter: Yes.

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2 Your CP for an alternate drug substance manufacturer states "There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change." A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that "Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance (b) (4) initially. In this case, the request to qualify the site for (b) (4) will follow at a later date."
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP's to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

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Reference ID: 2972073

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/s/

JANICE T BROWN
07/11/2011

SARAH P MIKSINSKI
07/12/2011

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number:	Supplement Number and Type:	Established/Proper Name:
202192	Original NDA	Ruxolitinib phosphate
Applicant:	**Letter Date:**	**Stamp Date:**
Incyte Corporation	03-Jun-2011	03-Jun-2011

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*				
	PARAMETER	**YES**	**NO**	**COMMENT**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
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
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

Reference ID: 2972079

B. FACILITIES*				
	PARAMETER	**YES**	**NO**	**COMMENT**
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

Reference ID: 2972079

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

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	

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.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		Expiry will be determined by primary reviewers in ONDQA/OBP
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

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

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		
I. Labeling				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

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J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N.A.
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		See attached

Comments for 74-Day Letter:

1. Your submission includes two proposed comparability protocols for an alternate drug substance and drug product manufacturer. Identify the proposed alternate drug substance and drug product manufacturer.
2 Your CP for an alternate drug substance manufacturer states "There will be no major manufacturing process modifications; no changes in acceptance criteria and no major changes to analytical methods for starting materials, intermediates, reagents and solvents involved. The scale of the drug substance manufacture will be comparable with the approved commercial scale. Equipment changes will be limited to those needed to accommodate the site change." A similar statement is included in your drug product CP. Revise your CP to fully describe all CMC changes for both manufacturers.
3. In your CP for the alternate drug substance manufacturer, specify the manufacturing process that will be used at the alternate manufacturing site. Your submission states that "Incyte may elect to file for an alternate site to manufacture the ruxolitinib phosphate drug substance using only (b) (4) initially. In this case, the request to qualify the site for (b) (4) will follow at a later date."
4. Revise your drug substance CP to include drug substance characterization analysis.
5. Your request for a proposed reporting category of a CBE-0 is not acceptable.
6. Each proposed CP is a stand alone submission. Revise your CP's to include all changes and acceptance criteria for each specified test to demonstrate equivalence between pre- and post-change material.

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APPEARS THIS WAY ON ORIGINAL

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{See appended electronic signature page}

Janice Brown Date: 22-Jun-2011
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D. Date: 22-Jun-2011
Chief, Branch 2
Division of Pre-Marketing Assessment 1
Office of New Drug Quality Assessment

Reference ID: 2972079

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

/s/

JANICE T BROWN
07/11/2011

SARAH P MIKSINSKI
07/12/2011