CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202192Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202192 SUPPL # HFD # 160

Trade Name Jakafi

Generic Name ruxolitinib

Applicant Name Incyte Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

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YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 for new molecular entity and 7 years for orphan drug designation

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

Reference ID: 3044845

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

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IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

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c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

INCB--351
INCB-352

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !
YES ☐ ! NO ☐
Explain: ! Explain:

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Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Amy Baird
Title: Regulatory Project Manager
Date: November 9, 2011

Name of Office/Division Director signing form: Edvardas Kaminskas, M.D.
Title: Deputy Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Reference ID: 3044845

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

/s/

AMY C BAIRD
11/15/2011

EDVARDAS KAMINSKAS
11/16/2011

3. DEBARMENT CERTIFICATION

Incyte Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Incyte Corporation

5/13/11
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202192 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Jakafi Established/Proper Name: ruxolitinib Dosage Form: tablets		Applicant: Incyte Corporation Agent for Applicant (if applicable):
RPM: Amy Baird		Division: CDER/OHOP/DHP

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. If no listed drug, explain. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ Other (explain) **Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.**

❖ Actions	
• Proposed action • User Fee Goal Date is 12/3/2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 1P ☒ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ REMS not required Comments:	
❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Press Release

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3048585

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 10/28/11

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☐ Yes ☐ No
*If "**Yes,**" skip to question (4) below. If "**No,**" continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No,**" continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No,**" the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No,**" continue with question (5).*	

Reference ID: 3048585

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	11-22-2011
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 11-16-2011
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	10-3-2011
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	9/7/2011 9/6/2011
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEPA 10/28/2011 ☒ DRISK 10/27/2011 ☒ DDMAC 10/19/2011 ☐ SEALD ☐ CSS ☒ Other reviews DDTCP 10/27/2011
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC N/A If PeRC review not necessary, explain: Application granted orphan designation • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	 ☐ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11-3-2010
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 11-16-2011
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11-15-2011
PMR/PMC Development Templates *(indicate total number)*	☐ None 11-15-2011
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	11-15-2011
• Clinical review(s) *(indicate date for each review)*	11-4-2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Reference ID: 3048585

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 9/16/2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 9/19/2011
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/27/2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 10/27/2011
• Supervisory Review(s) *(indicate date for each review)*	☐ None 10/27/2011
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/27/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 9/16/2011
❖ ECAC/CAC report/memo of meeting	☐ None Mtg 9/13/2011 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 10/21/2011
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 10/20/2011 (2 reviews)
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 8/23/2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Reference ID: 3048585

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/20/2011
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Reference ID: 3048585

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/s/

AMY C BAIRD
11/22/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, October 24, 2011 10:26 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA PMR/PMC Request

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

The Division of Hematology Products has determined that additional postmarketing information is required. Below are the PMR/PMCs for both efficacy and safety. We require Incyte's written agreement to commit to fulfill these requests as part of the FDA's review of your application. We encourage you to enhance the description further to improve the final product's data and evidence to be obtained. We may identify additional PMR/PMCs later in our review.

1.

NDA #/Product Name:	NDA 202192 Ruxolitinib	
PMC Description:	Commit to provide longer-term efficacy and safety outcomes of current clinical trials (INCB-351 and INCB-352) to provide at least 3 year follow-up data	
PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

2.

NDA #/Product Name:	NDA 202192 Ruxolitinib	
PMR Description:	Commit to provide safety findings related to the interval of drug discontinuation in at least 150 patients previously entered onto to INCB-351 and INCB-352 to determine if specific cautions are appropriate to describe discontinuation strategies.	
PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY
	Other:	MM/YYYY

3.

NDA #/Product Name:	NDA 202192 Ruxolitinib	
PMR Description:	Submit a protocol/plan to provide safety information on myelosuppression for up to 144 weeks of therapy following randomization in patients entered on INCB-351 and INCB-352 who are continuing on therapy past 24 and 48 weeks respectively	
PMR/PMC Schedule Milestones:	Preliminary Protocol Submission	MM/YYYY
	Final Protocol Submission:	MM/YYYY
	Study/Trial Completion:	MM/YYYY
	Final Report Submission:	MM/YYYY

Reference ID: 3033312

Other: _____ MM/YYYY

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
10/24/2011

Baird, Amy

From: Baird, Amy
Sent: Tuesday, October 18, 2011 12:33 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - OSE Completed Review of Container Label

Importance: High

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

The FDA's Office of Surveillance and Epidemiology has completed the review of the proposed labels for Jakafi and have the following comments. Please attempt to provide revised labels NLT COB October 21, 2011.

Container Label

1. Ensure the size of the established name is at least half as large as the letters comprising the proprietary name and has a prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2).

2. Revise the presentation of the established name to read “(Ruxolitinib) Tablets”. As currently presented as the salt form is inconsistent with the presentation of the strength statement in the base form.

3. Decrease the prominence of the ‘TM’ next to the proprietary name by using a smaller font.

4. Decrease the prominence of the color block that appears below the strength to allow for implementation of comment 1.

5. Decrease the prominence of the “Rx only” statement by un-bolding and using a smaller font.

6. Revise the statement “Dosage and Use: See Package Insert” to read “Usual Dosage: See Prescribing Information”.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3030521

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/s/

AMY C BAIRD
10/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192 **INFORMATION REQUEST**

Incyte Corporation
Attention: Ronald Falcone, Ph.D.
Vice President, Regulatory Affairs
Experimental Station
Rt. 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for JAKAFI™ (ruxolitinib) tablets.

We also refer to your September 27, 2011 submission, containing Chemistry, Manufacturing and Controls (CMC) information in response of an information request dated September 16, 2011.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For container labeling:

1. Revise the drug name from "JAKAFI™ (ruxolitinib phosphate) tablets" to "JAKAFI™ (ruxolitinib) tablets", as the strengths of the drug product are based on the ruxolitinib free base.

2. Revise the storage condition on container labels as follows:

   Store at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

3. Revise the name in the Structured Product Labeling (SPL) to "ruxolitinib tablets" from "ruxolitinib phosphate tablets".

For drug product container/closure system,

4. Provide USP <671> test results. Also, ensure the inner seal is removed prior to testing. Refer to *Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999 (Section III.D).* We note that in your 27-Sep-2011 response to comments No. 5 (b) under drug product in Agency's information request of 16-Sept-2011, USP <661> test results were provided, but USP <671> test results were not included.

Follow up comments for the Response to Information Request #3 dated 27-Sep-2011,

5. Provide in a tabular format the batch number and batch size for all the common blends from which subsequent batches of tablets across five different strengths were manufactured in section 3.2.P.5.4 in Tables 3, 4, and 5 with the phase 3/commercial formulation. In your response, you did not specify the batch number and batch size for (b) (4)

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
10/04/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, October 03, 2011 10:56 AM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA Pharm/Tox Request for Information

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the Pharmacology/Toxicology review team, please provide a response to the following requests for information.

1. Indicate whether the impurities (b) (4) (b) (4) were present in the 26-week Tg.rasH2 carcinogenicity study.

2. What were the levels of these impurities if they were present in the carcinogenicity study.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3023770

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/s/

AMY C BAIRD
10/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

METHODS VALIDATION MATERIALS RECEIVED

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880

Dear Ronald C. Falcone, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg and to our 9/13/2011 letter requesting sample materials for methods validation testing.

We acknowledge receipt on 9/28/2011, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
09/28/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 22, 2011 3:34 PM
To: Ronald Falcone
Subject: NDA 202192 Jakafi - FDA Clinical Pharmacology Request

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the Clinical Pharmacology review team, please provide a response to the following requests for information NLT COB September 28, 2011.

- We note your clinical pharmacology highlights report states "After a single oral dose of 14C-INCB018424, the terminal t½ of total drug-related material (ruxolitinib + metabolites) in plasma was 5.8 h (CV = 13%) (Study [INCB 18424-134]);" however we are unable to find this analysis in the report for Study [INCB 18424-134]. Please provide the location of this information or submit this analysis.

- It appears that sample stability following long term frozen storage for assay's DMB-07.111.1 and DMB-10.14.1 was not reported. Please confirm whether or not this was assessed. If it was please provide the location of this information or submit it.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3019206

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/s/

AMY C BAIRD
09/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192 **INFORMATION REQUEST**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D
Vice President, Regulatory Affairs
Rt. 141 & Henry Clay Road
Building 336
Wilmington, Delaware 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by (b) (4)[1] The pervasiveness and egregious nature of the violative practices by (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at (b) (4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or "prep" run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or "prep" runs that prevented (b) (4) and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by (b) (4) (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

---

(b) (4)

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by [redacted] (b) (4) during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Janet Jamison, Regulatory Project Manager, at (301) 796-2313.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Research and Evaluation

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/s/

ANN T FARRELL
09/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192 **INFORMATION REQUEST**

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Rt. 141 & Henry Clay Road, E336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets.

We also refer to your June 3, 2011, July 8, 2011, August 1, 2011, August 30, 2011 submissions, containing Chemistry, Manufacturing, and Control section of your NDA.

We are reviewing the Chemistry, Manufacturing, and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. For all proposed starting materials, provide the following information in Section 3.2.S.2.3:
   (a) A detailed description of the impurity profile.
   (b) Data from purging studies as generated by using impurities in the proposed starting materials, at levels higher than those proposed in the starting material specifications. The data should adequately demonstrate the ability of the manufacturing process to remove and control impurities that may be present in the proposed starting materials at the desired levels in the drug substance.
   (c) Justification of the starting material specifications based on the results from purging studies.
   (d) Change control strategies for any potential revisions to the manufacture of the proposed starting materials including the vendor's reporting of any changes in starting material specifications or control.

2. For the specification for Intermediate [redacted] (b) (4) (Section 3.2.S.2.4), establish acceptance criteria and incorporate specifications for assay and achiral purity. Include a justification for the proposed limits.

3. Include testing for residue on ignition in the drug substance specification. Your justification for omitting this test, as provided in Section 3.2.S.4.5, is not acceptable.

4. For the drug substance specification (Table 1, Section 3.2.S.4.1), designate only one analytical procedure (either IC/018424/024 or IC/018424/033) as the regulatory method for the determination of phosphate content. The other method can be designated as an alternate method. Revise and submit the drug substance specification accordingly.

5. In Section 3.2.S.6 for the drug substance packaging materials, provide specific 21 CFR citations indicating compliance with 21 CFR requirements for direct food contact.

Drug Product

1. Provide in a tabular format the formulation number and composition for Batch 1399-2644-RD-3B (10 mg), Batch 1399-2644-RD-2B (15 mg), Batch 1399-2493-RD-sublot 2 (20 mg) and Batch 399-2612-R-18KP (25 mg) for studies described in section 3.2.P.2.2.1.2.

2. In addition to the 5 mg tablet strength (Tables 3 and 4; Module 3.2.P.2, page 5), provide similar comparative multipoint dissolution profile data (mean, individual, and plots) for the 25 mg tablet strength manufactured using formulation 18424-001-00 and formulation 18424-007-00 in order to encompass the entire tablet strengths.

3. [redacted] (b) (4)

4. Submit data demonstrating that [redacted] (b) (4)

5. Provide the following for the container/closure system:
   (a) Confirmation that all packaging components (in section 3.2.P.7.1) conform to appropriate CFR food additive regulations. Provide specific 21 CFR references for each component.
   (b) USP <661> and <671> testing results.

6. Provide test results from identification, assay, and degradation product analysis for the nasogastric tube compatibility study and for the tablet (aqueous suspension) stability study to support the proposed maximum hold period.

7. Provide an explanation for the decrease in dissolution (5 min, 15 min, and 30 min) for certain lots [e.g., Lot A51341B (25 mg) and Lot A51342B (25 mg)].

8. Provide comparative data for the 5 mg and 25 mg tablets that indicates the correlation between tablet hardness, [redacted] (b) (4) and dissolution at different time points of the stability studies.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
09/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

REQUEST FOR METHODS VALIDATION MATERIALS

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880

Dear Ronald C. Falcone, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg.

We will be performing methods validation studies on Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg and 25 mg, as described in NDA 202192.

In order to perform the necessary testing, we request the following sample materials and equipments:

<u>Sample</u>
30 -- Ruxolitinib Phosphate Tablets, 5 mg/ tablet
300 mg - INCB018424 Phosphate Drug Substance

<u>Standards</u>
500 mg INCB018424 Phosphate Reference Standard

(b) (4)

(b) (4)

(b) (4)

[redacted]

Equipment

1 - Zorbax Eclipse XDB-C18, 3.5 µm, 4.6 x 150 mm
1 - Zorbax SB-C18, 3.5 µm, 4.6 mm x 150 mm
1 - Chiralcel OD, 10 µm, 250 x 4.6 mm

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James F. Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (James.Allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James F. Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

JAMES F ALLGIRE
09/13/2011

Baird, Amy

From: Baird, Amy
Sent: Thursday, September 08, 2011 2:14 PM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA Pharm/Tox Requests

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the pharmacology/toxicology review team, please provide a response to the following requests for information.

We note that you have not provided the complete data for the Ames tests conducted with the impurities. For evaluation of the mutagenicity potential of the 6 impurities with structural aler (b) (4) (b) (4) please submit the study reports of Ames tests with detailed information, such as the basis for selection of concentrations and the number of colonies under the conditions tested.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3012235

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/s/

AMY C BAIRD
09/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Incyte Corporation
Rt. 141 & Henry Clay Road
Building E336
Wilmington, Delaware 19880-0336

ATTENTION: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruxolitinib Phosphate Tablets, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg.

We also refer to your June 10, 2011, correspondence, received June 10, 2011, and your August 4, 2011, amendment, received August 4, 2011, requesting review of your proposed proprietary name, Jakafi. We have completed our review of the proposed proprietary name, Jakafi and have concluded that it is acceptable.

The proposed proprietary name, Jakafi, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 10, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Amy Baird at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/07/2011

Baird, Amy

From: Baird, Amy
Sent: Friday, August 26, 2011 4:18 PM
To: Ronald Falcone; 'Neil Wummer'
Subject: NDA 020192 Ruxolitinib - Request regarding Container Labels

Ron and Neil,

Please refer to the NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis." We also refer to your submission dated August 28, 2011, which provided a clearer image of the container labels.

There seems to be some discrepancy as to which carton and container labels are the correct version that Incyte will be using to market the product. For instance...

(b) (4)

In order to confirm which are the correct labels, please officially submit a letter confirming the correct color of the labels and also provide another copy of these labels. Please do not make reference to any previous submissions in your response.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3007082

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/s/

AMY C BAIRD
08/26/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, August 17, 2011 11:36 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA Request for Better Resolution Carton/Container Labels

Ron,

Please refer to the NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis." We also refer to your submission dated August 5, 2011, providing a response to the FDA August 3, 2011, e-mail requesting better quality images of the container/carton labels.

The FDA team has reviewed your August 5, 2011, submission and still find the images difficult to read. Please provide mock-ups of the proposed container/carton labels as an electronic submission to your NDA, but also provide a paper copy of the labels directly to myself via courier. Please send the paper copy to the address below.

Amy Baird
Food and Drug Administration
10903 New Hampshire Ave.
WO #22, Room 1223
Silver Spring, MD 20993

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 3001959

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/s/

AMY C BAIRD
08/17/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, August 03, 2011 2:52 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - Labeling Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, provide responses to the following requests for information.

The images of the container labels submitted in both the Proprietary Name Request dated June 10, 2011, and in the original NDA submission are not legible. Can you please submit a better quality/readable images of the container labels. Perhaps a better resolution image or mock up samples?

Please submit this NLT COB August 8, 2011.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 2983396

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/s/

AMY C BAIRD
08/03/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202192

FILING COMMUNICATION

Incyte Corporation
Attention: Ronald C. Falcone, Ph.D.
Vice President, Regulatory Affairs
Route 141 & Henry Clay Road
Building 336
Wilmington, DE 19880-0336

Dear Dr. Falcone:

Please refer to your New Drug Application (NDA) dated June 3, 2011, received June 3, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ruxolitinib Phosphate Tablets.

We also refer to your amendments dated June 10, July 8 and 12, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 3, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 4, 2011.

We request that you submit the following information:

1. Regarding Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

2. 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.

3. 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.

4. 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."

5. Revise your drug substance CP to include drug substance characterization analysis.

6. Your request for a proposed reporting category of a CBE-0 is not acceptable.

7. 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.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Acting Director
Division of Hematology Drug Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
08/02/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, August 01, 2011 2:36 PM
To: 'Ronald Falcone'
Subject: RE: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Ron,

Thank you for the email below.

Per the request of the FDA review team, please identify the name of the dataset (one dataset) that is one record per patient and includes primary endpoint, secondary endpoints, patient demographics and disposition for Study 352. This dataset should be similar in structure to 'ASEFF2.xpt' for Study 351.

Thanks,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Ronald Falcone [mailto:rfalcone@incyte.com]
Sent: Friday, July 29, 2011 10:01 AM
To: Baird, Amy
Subject: RE: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Dear Amy,

In response to your email of July 27, 2011, which contained requests from CMC, Clinical Pharmacology, and Biometrics regarding the review of NDA 202192, I have attached responses. Incyte plans to provide the formal eCTD response in the near future.

Please let me know if you have questions.

Kind Regards,
Ron

Ron C Falcone, PhD
Vice President, Regulatory Affairs
Incyte Corporation
E400/6220A
Rt 141 & Henry Clay Rd
Wilmington, DE 19880

Work: 302-498-6846
Mobile: 610-457-2258

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: Wednesday, July 27, 2011 11:28 AM
To: Ronald Falcone
Subject: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Ron,
Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, please provide responses to the following requests for information.

Chemistry, Manufacturing, and Controls (CMC)

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.

Biometrics

For Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

Clinical Pharmacology

We note that in the dataset recently provided for study DMB-10.55.1 the reported exposure (aucinf, AUClast, Cmax) for the parent compound (INCB018424) for each subject differs from that reported for the same subjects in Study INCB 18424-137 (see attached). Please provide the following: a rationale for this discrepancy, whether a similar discrepancy should be expected for other metabolite studies evaluated as part of the DMB-10.55.1 study, and how the sponsor believes the metabolite to parent ratios reported in DMB-10.55.1 should be interpreted in light of this discrepancy.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager

Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
08/01/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, August 01, 2011 2:26 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA Clinical Request for Information

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, provide responses to the following requests for information. Please provide the response NLT August 12, 2011.

Please provide the following information in a list of all patients on INCB-351 and INCB-352 who achieved a ≥ 35% reduction of spleen volume (for each patient individually) on the ruxolitinib arms:

1. Date of initiation of ruxolitinib therapy, patient identification number from NDA 202192.
2. Date of achievement of ≥35% reduction of spleen volume
3. Interval between the time of achievement of ≥35% reduction of spleen volume and the time of data lock for the submission of NDA 202192 on June 3, 2011 (if the patient had not progressed by the time of data lock).
4. Interval between the time of achievement of ≥35% reduction of spleen volume and the time of a regrowth of the spleen volume by 25% from the nadir (if that occurred) if that occurred before the data lock before the June 3, 2011 submission of the NDA 202192.

Please provide similar information for INCB-351 patients on the ruxolitinib arm who achieved a reduction of Total Symptom Score ≥50% (for each patient individually).

1. Date of initiation of ruxolitinib therapy, patient identification number from NDA 202192 and the patient identification number from NDA 202192.

2. Date of achievement of a reduction by ≥50% of the Total Symptom Score

3. Interval between the time of achievement of reduction by ≥50% of the Total Symptom Score and the time of data lock for the submission of NDA 202192 on June 3, 2011 (if the patient had not progressed by the time of data lock).

4. Interval between the time of achievement of ≥50% of the Total Symptom Score and the time of progression if that occurred before the time of data lock prior to the June 3, 2011 of the NDA 202192, along with the criteria used to define progression of symptoms after achieving a reduction of ≥50% of the Total Symptom Score.

Please do not hesitate to contact me should you have any questions.

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

Reference ID: 2982073

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/s/

AMY C BAIRD
08/01/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, July 27, 2011 11:28 AM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA CMC, Clinical Pharmacology, and Biometrics requests

Attachments: study137vsdmb10551.pdf

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the FDA review team, please provide responses to the following requests for information.

Chemistry, Manufacturing, and Controls (CMC)

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.

Biometrics

For Study 352, provide a one record per subject dataset including primary, secondary endpoints, patient demographics and disposition.

Clinical Pharmacology

We note that in the dataset recently provided for study DMB-10.55.1 the reported exposure (aucinf, AUClast, Cmax) for the parent compound (INCB018424) for each subject differs from that reported for the same subjects in Study INCB 18424-137 (see attached). Please provide the following: a rationale for this discrepancy, whether a similar discrepancy should be expected for other metabolite studies evaluated as part of the DMB-10.55.1 study, and how the sponsor believes the metabolite to parent ratios reported in DMB-10.55.1 should be interpreted in light of this discrepancy.

study137vsdmb105
51.pdf (11 KB)...

Reference ID: 2979536

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
07/27/2011

Baird, Amy

From: Baird, Amy
Sent: Tuesday, July 12, 2011 10:44 AM
To: 'Ronald Falcone'
Subject: RE: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Thank you for your email below which provides a response to the FDA Clinical Pharmacology requests.

Per the Clinical Pharmacology review team, please provide a response to the following:

Please clarify if the phrase "data was not generated" in your response 3.5.1 should be taken to mean the samples were not collected all, collected but not bioanalyzed, or bioanalyzed but not incorporated into the statistical/PK analysis plan.

While we note your argument regarding the importance of protein binding, we are not persuaded by it. If the raw data for unbound concentrations in the renal and hepatic studies exist please submit it in SAS transport format with additional variables that would allow a summary by impairment class and merging with other data sets to include other pertinent variables that have already been submitted.

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

From: Ronald Falcone [mailto:rfalcone@incyte.com]
Sent: Thursday, July 07, 2011 2:52 PM
To: Baird, Amy
Subject: RE: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Dear Amy,

In response to your email of June 29, 2011, which contained requests from the Clinical Pharmacology review team, Incyte will provide a full eCTD response with all requested data sets by Tuesday July 12. In advance of the full formal submission, I have attached 2 pdf files: the 1st file provides textual responses to questions (raw data sets for questions #1 and #8 will accompany the eCTD response); the 2nd file contains the study report (CMC 11.11.1) for the nasogastric tube study, which was requested in question #1.

Please let me know if I can be of further assistance.

Kind regards,
Ron

Ron C Falcone, PhD
Vice President, Regulatory Affairs
Incyte Corporation
E400/6220A
Rt 141 & Henry Clay Rd
Wilmington, DE 19880

Work: 302-498-6846
Mobile: 610-457-2258

From: Baird, Amy [mailto:Amy.Baird@fda.hhs.gov]
Sent: Wednesday, June 29, 2011 1:08 PM
To: Ronald Falcone
Subject: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the clinical pharmacology review team, please provide a response to the following requests for information within 10 business days. If this information has already been submitted, please provide the location within the eCTD.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3. (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
    a. DMB-10.43.1
    b. DMB-10.55.1
    c. DMB-06.168.1

d. IN VITRO-11.01.1

7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1
9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
    e. Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define.PDF file
    f. Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define.PDF file

Please do not hesitate to contact me should you have any questions.

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

****
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/s/

AMY C BAIRD
07/12/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, June 29, 2011 3:23 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - FDA CMC Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the CMC review team, please provide a response to the following requests for information within 14 business days.

1. Under Module 3.2.P.2.2, Section 2.1.2.2 (p.5), you provided the dissolution data of the 5 representative batches, 5 mg (Lot A53228), 10 mg (Batch 1399- 2644-RD-3B), 15 mg (Batch 1399-2644-RD-2B), 20 mg (Batch 1399-2493-RD-sublot 2), and 25 mg (Batch 399-2612-R-18KP) tablets strengths in three dissolution media, 0.1 N HCl, and pH 4.5 and pH 6.8 buffer.

   You reported that the 5 mg (the reference drug product and the Phase-3 biobatch), 10 mg, 15 mg, 20 mg, and 25 mg strengths exhibit rapid (b) (4) of the drug dissolved in < 15 min in each of the three dissolution media) and similar dissolution profiles. However, the lot/batch manufacturing information on the 4 higher strengths could not be located in the NDA (except for the size of the 5 mg biobatch A53228; M3.2.P.8.1, Table 4, p.4).

   Therefore, please provide the needed information (manufacturing date, site, and batch size) on the 4 higher strengths for review so that the proposed specifications (Q= (b) (4) at 30 min) using the proposed dissolution method, USP 2 (paddle) with 50 rpm in 0.1 N HCl medium can be evaluated.

2. You requested the Agency's review on your IND amendment (SN-235) dated 01/17/11 for the CMC investigational study protocol entitled:

   "Evaluation of Stability and Dosing of Ruxolitinib Phosphate (INCB018424 Phosphate) Tablets as Suspension to Support Nasogastric Administration"

   The Agency reviewed the protocol and forwarded the comments to you on 05/27/11. Please respond to the Agency's comments and provide your justifications for the results of the above *in vitro* stability study (already submitted in the NDA) to support the Nasogastric administration of your product.

Please do not hesitate to contact me should you have any questions.

Regards,

Reference ID: 2967772

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
06/29/2011

Baird, Amy

From: Baird, Amy
Sent: Wednesday, June 29, 2011 1:08 PM
To: 'Ronald Falcone'
Subject: NDA 202192 ruxolitinib - FDA Clinical Pharmacology Request

Ron,

Please refer to your NDA application for NDA 202192 Ruxolitinib Phosphate Tablets dated June 3, 2011, which provides for the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Per the request of the clinical pharmacology review team, please provide a response to the following requests for information within 10 business days. If this information has already been submitted, please provide the location within the eCTD.

1. Please provide a complete study report and raw data set in electronic format (i.e., SAS transport files) for the Nasogastric tube study summarized in Section 1.4 of module 3.2.P.8
2. Please provide a table listing the different tablet formulations used in the various human clinical studies or affirm that the to-be-marketed image was used in all studies.
3. (b) (4)
4. Please confirm that the formulation used in the food effect sub- study in study INCB 18424-131 was the to-be-marketed formulation.
5. We note in both your hepatic impairment (INCB 18424-137) and renal impairment (INCB 18424-142) studies that the fraction unbound parameter was part of your PK analysis plan yet these data are not present in your report or your raw data sets. Please provide your analysis of this parameter and the respective raw data set in electronic format (i.e., SAS transport files) for each of these studies. If this information has already been submitted please provide the location in the eCTD.
6. Please provide the raw data set in electronic format (i.e., SAS transport files) for each of the following studies:
   a. DMB-10.43.1
   b. DMB-10.55.1
   c. DMB-06.168.1
   d. IN VITRO-11.01.1
7. Please provide file definitions for the raw datasets associated with study INCB 18424-251
8. Please provide the Provide Bioanalytical Report(s) for studies DMB-10.43.1 and DMB-10.55.1
9. We noticed that you submitted the dataset for PopPK analysis and PK/PD analyses. Please submit the each PK and PD datasets for each clinical study and the programs you used to support the individual PK analysis in each study.
10. In PopPK dataset, please clarify the difference regarding the coding for the following variables:
    a. Variable "HEPCLS": both 2 and 3 are coded for "Mild impairment" in the Define.PDF file
    b. Variable "CYPInd" both 3 and 4 are coded for "weak inducers" in the Define.PDF file

Please do not hesitate to contact me should you have any questions.

Reference ID: 2967593

Regards,

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

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/s/

AMY C BAIRD
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: QT/IRT Team Interdisciplinary Review Team
Attention: Devi Kozeli

FROM (*Name, Office/Division, and Phone Number of Requestor*): Amy Baird, Division of Drug Oncology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6-29-2011		202192	New NDA	6-3-2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ruxolitinib			8-29-2011

NAME OF FIRM: Incyte Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA 202192 Ruxolitinib is a new NDA submitted with the proposed indication "treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis."

Within the NDA submission are the study results of the trial entitled "An Assessment of Heart Rate Corrected QT Intervals in Healthy Subjects Dosed with Single Doses of INCB018424 Compared with Moxifloxacin." Please review. Below is a link to the NDA submission.

\\CDSESUB1\EVSPROD\NDA202192\202192.ENX

MOR: Dr. Albert Deisseroth
Clin Pharm: Dr. Joseph Grillo
RPM: Amy Baird

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☐ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

AMY C BAIRD
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff** ***E-mail to:*** **CDER OPS IO MICRO** ***Paper mail to:*** **WO Bldg 51, Room 4193**	FROM: Tu-Van Lambert, Product Quality RPM, Office of New Drug Quality Assessment, WO 21 Room 2625, (301) 796-4246 PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 29, 2011		202192	Electronic new NDA	June 3, 2011

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE	DESIRED COMPLETION DATE
Ruxolitinib phosphate tablets	Priority (very)	December 3, 2011	September 3, 2011

NAME OF APPLICANT OR SPONSOR: Incyte Corporation

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: August 1, 2011
- ☐ BUNDLED
- X DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

Micro reviewer requested to review micro and chirality tests that have been removed from the NDA from what was included in referenced IND 077456. Clinical requests this NDA to be a super priority NDA review.

Link to application: \\Cdsesub1\evsprod\nda202192

SIGNATURE OF REQUESTER Tu-Van Lambert	REVIEW REQUEST DELIVERED BY (Check one): X DARRTS ☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND DOCUMENTS FOR REVIEW DELIVERED BY (Check one): X EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

TU-VAN L LAMBERT
06/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Baird, Regulatory Project Manager, Division of Hematology Products, 301-796-4969

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
6/20/2011		202192	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Ruxolitinib Phosphate Tablets			9/9/2011

NAME OF FIRM: Incyte	PDUFA Date: 12/4/2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ✓ PACKAGE INSERT (PI)
- ✓ PATIENT PACKAGE INSERT (PPI)
- ✓ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ✓ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ✓ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:
Mid-Cycle Meeting: 8/4/2011

Labeling Meetings: 8/11/2011, 8/17/2011, 8/18/2011, 8/22/2011, 8/31/2011, 9/1/2011, 9/7/2011, 9/8/2011, 9/16/2011

Wrap-Up Meeting: 9/19/2011

Below is the EDR link to the original submission:
\\CDSESUB1\EVSPROD\NDA202192\202192.ENX

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

AMY C BAIRD
06/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADM NISTRATION	REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE (Attention: Sue Kang)**	FROM: Amy Baird, Regulatory Project Manager, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
6/20/2011		202192	New NDA	6/3/2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ruxolitinib Phosphate Tablets			8/17/2011

NAME OF FIRM: Incyte

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Requesting OSE review of labeling associated with this New Drug Application (new NME) which provides for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

We ask that OSE attend all pertinent review meetings (labeling, team meetings).

MOR= Dr. Albert Deisseroth
RPM= Amy Baird

EDR link is below

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

AMY C BAIRD
06/20/2011

Baird, Amy

From: Baird, Amy
Sent: Monday, June 20, 2011 2:08 PM
To: 'Ronald Falcone'
Subject: NDA 202192 Ruxolitinib - Sponsor NDA Presentation

Ron,

The FDA review team would like Incyte to give an NDA presentation for Ruxolitinib (very similar to an Advisory Committee presentation). The information below will help Incyte in the preparation of the presentation.

The possibe dates for scheduling the presentation are 7/8, 7/15, 7/18, 7/22, or 7/25 (if the presentation falls on a Monday Incyte would present in the morning and if on a Friday presentation would be in the afternoon). Also, you will need to provide a copy of the presentation a couple of days prior to the scheduled meeting. The presentation would be attended by the Office Director, Division Director, and the remaining review team members, but also is open for all Divisions to attend (all Divisions under the Office of Oncology Drug Products).

Regards,
Amy

Amy Baird
Regulatory Project Manager
Division of Hematology Products, CDER, FDA
10903 New Hampshire Ave
WO #22, Room 1223
Silver Spring, MD 20993
Telephone: 301-796-4969
Facsimile: 301-796-9845
Email: amy.baird@fda.hhs.gov

OODP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OODP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your

application or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees

2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.

4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.

5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.

6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.

7. Regulatory history, including the following:
   - Orphan Drug designation, Fast Track designation
   - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
   - Key Outcomes from FDA Interactions
     - EOP2 Meeting
     - Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
     - Pre-NDA/BLA meeting
     - Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

   You should also present results of the following, as appropriate:
   - Clinical study sites (foreign or domestic)
   - Biomarker development for population selection (if applicable)
   - Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data

10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
    - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.

11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities

12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).

13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU).

14. Risk/benefit profile for drug/biologic

15. Summary

16. Q & A

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/s/

AMY C BAIRD
06/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077456

MEETING MINUTES

Incyte Corporation
Attention: Yung-Ao Hsieh, Ph.D.
Senior Director, Regulatory Affairs CMC
Route 141 & Henry Clay Road, Building 400
Wilmington, DE 19880

Dear Dr. Hsieh:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INCB018424.

We also refer to the meeting between representatives of your firm and the FDA on November 30, 2010. The purpose of the meeting was to discuss the CMC information for the INCB018424 phosphate immediate release tablets of 5,10,15,20, 25 mg strengths.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Project Manager at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-NDA (CMC)
Meeting Date and Time:	Tuesday, November 30, 2010
Meeting Location:	White Oak Building 22, Conference Room: 1415
Application Number:	IND 077456
Product Name:	INCB018424
Indication:	treatment of patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)
Sponsor/Applicant Name:	Incyte Corporation
Meeting Chair:	Sarah Pope Miksinski, Ph.D.
Meeting Recorder:	Tu-Van Lambert, M.S.

FDA ATTENDEES

Sarah Pope Miksinski, Ph.D. – Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), Office of New Drug Quality Assessment (ONDQA)
Janice T. Brown, M.S. – CMC Lead, DNDQA I, ONDQA
Joyce Z. Crich, Ph.D. – Product Quality Reviewer, Branch II, DNDQA I, ONDQA
Edvardas Kaminskas, M.D. – Deputy Division Director, Division of Hematology Products (DHP), Office of Oncology Drug Products (OODP)
Albert Deisseroth, M.D. – Medical Officer, DHP/OODP
Tu-Van Le Lambert, M.S. – Product Quality Regulatory Project Manager, DNDQA I, ONDQA

SPONSOR ATTENDEES

Ronald C. Falcone, Ph.D - Vice President, Regulatory Affairs, Incyte Corporation
Yung-Ao Hsieh, Ph.D. - Senior Director, Regulatory Affairs, CMC, Incyte Corporation
Carl Longfellow - Senior Director, Project Management, CMC, Incyte Corporation
Bhavnish Parikh, Ph.D. - Executive Director, Pharmaceutical Development, Incyte Corporation
Jay Shukla, Ph.D. - Vice President, CMC, Incyte Corporation
Chris Koval – Executive Director, QA GMP/GLP, Incyte Corporation
Joe Zhou, Ph.D. - Executive Director, Process Chemistry, Incyte Corporation
Rich Levy, MD – Executive Vice President, Chief Drug Development and Medical Officer, Incyte Corporation

Rose-Marie Dannenfelser - Director, Technical R&D, Novartis Pharmaceuticals Corporation
Donna Kapples, M.S. - Associate Director, Regulatory CMC, Novartis Pharmaceuticals Corporation

1.0 BACKGROUND

INCB018424 phosphate, a sytnehtic inhibitor of the JAKs kinases, is developed for the treatment of patients with myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythemia-myelofibrosis (PET-MF). The Sponsor plans to submit a New Drug Application (NDA) during the second quarter of 2011. To prepare for this submission, the Sponsor requested in this meeting to discuss the CMC information for the INCB018424 phosphate immediate release tablets of 5,10,15,20, 25 mg strengths to obtain guidance on content of the Quality section of the eCTD for submission.

2. DISCUSSION

Preliminary responses from the Agency were sent on November 12, 2010. Based on these preliminary responses, the Sponsor requested further discussion of Questions 1, 2, 4, 5 and 9. These questions are included in the discussion below. Questions provided by the Sponsor are ***Bold Italics***, FDA Responses provided in preliminary comments are in Regular, discussion items during the meeting are in *Italics*.

2.1. DRUG SUBSTANCE

Designation of Starting Materials for Drug Substance Synthetic [redacted]
Question 1:

Incyte has discussed the company's position on designated starting materials for drug substance synthesis with the Division in EOP 2 CMC meeting (dated December 3, 2008) and Type C CMC meeting (dated July 7, 2009). Your Preliminary Response (dated July 8, 2009) has advised that the Division will consider the acceptability of [redacted] as potential starting materials. Incyte is proposing [redacted] as the designated starting materials for synthetic [redacted]. The justification for the designated starting materials and their controls are provided in Drug Substance, Section 2.3.1, Control of Materials (Attachment 1). Does the Division accept these three compounds as the designated starting materials for [redacted]

Agency Response:

Your proposed starting materials [redacted] appear to be reasonable. In the NDA, also include the following to support the use of these compounds as starting materials:

1. A detailed description of the impurity profile.
2. Brief description of synthetic strategies and methods of manufacture.
3. Detailed discussion on carry-forward impurities.
4. Controls and analytical methods to separate and measure appropriate impurities.
5. Supplier information for the starting materials.

6. Information on impurity fate studies. Detailed discussion on purging studies to demonstrate the ability of the manufacturing process to remove and control the impurities from the starting materials to the desired levels.
7. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.

Discussion: **None**

Recycle of [redacted] for the Manufacture of the Drug Substance [redacted]
Question 2:

[redacted] ***Based on the recommendations from the Division (CMC EOP2 FDA Meeting Minutes, dated January 2, 2009), supporting data provided in Drug Substance, Section 2.2.2, Description of Synthetic [redacted] (Attachment 1) include:***

1. ***In-process specifications and batch analytical data for [redacted]***
2. ***Detailed description of [redacted]***
3. ***Certificate of Analysis of drug substance Lot 08-340-002 manufactured using [redacted]***
4. ***Comparison of batch analysis data of drug substance Lot 09-340-003 [redacted] and Lot 08-340-002 [redacted]***
5. ***Stability data of Lot 08-340-002 at 25°C/60% RH (12 months) and at 40°C/75% RH (6 months)***
6. ***Certificate of Analysis of drug product Lot A48107 (5 mg strength) manufactured from drug substance Lot 08-340-002***
7. ***Comparison of batch analysis data of drug product Lot A45578 (manufactured from drug substance Lot 08-340-001R, [redacted]) and Lot A48107 (manufactured from drug substance Lot 08-340-002)***

Additionally, the process validation report for [redacted] (including full validation of the [redacted] (b) (4)) and executed batch record of a representative batch manufactured using [redacted] will be provided in the NDA.

Does the Division agree that there are adequate data, and no additional studies are needed, to establish the equivalency between the drug substance batches manufactured using either [redacted]?

Agency Response:

No. In addition to the information listed above, also include the following in your NDA:

Drug Substance

1. Comparative batch analysis for two additional drug substance lots (three lots total) manufactured using [redacted]

2. Six months comparative accelerated and available long-term stability data for two additional lots of drug substance manufactured using [redacted]

Drug Product

3. Comparative batch analysis including multi-point dissolution profiles (e.g., 15, 30, 45, 60 and 120 minutes or until the asymptote is reached) of drug product using the drug substance manufactured by [redacted].
4. Three months comparative accelerated stability for the highest and lowest tablet strength using drug substance manufactured by process [redacted]

Other

5. Specify the number of recycle operations can be performed on the same batch of intermediate ([redacted].
6. Include purity and impurity limits in the proposed specification for [redacted]

Discussion:

- *The agency requested a detailed description of the recycling operation that includes how many times the* [redacted] *pool would be recycled, specifications for the pool, and characterization analysis.*
- *The Sponsor explained that the* [redacted]
- *As previously agreed during the End-of-Phase 2 CMC meeting, the Sponsor stated that* [redacted] *s would be submitted at the time of NDA filing. When they intend to submit the NDA in May 2011, the Sponsor should have three month accelerated stability data for two additional lots available. In this submission scenario the Sponsor would commit to submitting amendments at the Agency's guidance. If they have to submit six-month accelerated stability data at the time of NDA filing, they would not be able to file the NDA until August 2011.*
- *The Agency requested that the Sponsor submit a submission proposal with alternate scenarios based on the availability of their stability data. The Sponsor agreed to do so.*

Drug Substance Specification
Question 3:

The proposed specification for INCB018424 phosphate drug substance with supporting data and justifications are provided in Drug Substance, Section 4, Control of Drug Substance (Attachment 1). Does the Division agree that the proposed specification is adequate to ensure the identity, strength, quality and purity of the INCB018424 phosphate drug substance?

Agency Response:

Your proposed specifications for INCB018424 appear to be reasonable provided that any unspecified impurities are below the threshold limits listed in Q3A -Impurities In New Drug Substances. The final determination on the adequacy of the proposed drug substance specification is a review issue and will be determined during the evaluation of your NDA. We note that you have not proposed an in-process control or drug substance specification for particle size distribution. Provide adequate justification for this proposal (see ICH Q6A Decision tree #3) in your NDA.

Discussion: **None**

2.2. DRUG PRODUCT

Drug Product Specifications for Tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg Strengths
Question 4:

The proposed specification for INCB018424 phosphate drug product tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths with supporting data and justifications are provided in Drug Product, Section 5, Control of Drug Product (Attachment 2). Does the Division agree that the proposed specification is adequate to ensure the identity, strength, quality and purity of the INCB018424 phosphate drug product tablets?

Agency Response:

In general, your proposed specifications appear reasonable; however, a final determination will be made after reviewing the data in the NDA submission. Your justification for omitting the stereospecific identity test will be a review issue.

Additional Comments:

- **Dissolution Method:** Please provide in your NDA submission the dissolution method report including the complete dissolution profile data collected during the development and validation of the proposed dissolution method. A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as the most optimal, should be provided in the report. The dissolution profile should be complete and cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable. The dissolution/release data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug eluted with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.

  The method's validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that may have an effect on the dissolution of the drug should also be included in the report. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for the testing of the final product. Include

the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the method (i.e., method robustness, etc.) and assay (precision, accuracy, linearity, stability, etc.). The selected method should be discriminatory and sensitive enough to reject lots that would have less than acceptable clinical performance.

- **Dissolution Acceptance Criterion:** The provided dissolution data indicate a very fast dissolution for your product. Therefore, the proposed acceptance criterion of Q= at 30 minutes may not be adequate for your product. Provide in your NDA submission the dissolution profile data from the clinical and stability batches supporting the selection of this criterion (i.e., specification-sampling time point and specification value). In general, for immediate release product the selection of the specification time point should be where Q=(b) (4) dissolution occurs.

- **BA/BE Waiver Request:** When several strengths of the same dosage form are proportionally similar in their active and inactive ingredients, an in vivo waiver can be given for one or more than one lower strengths based on comparability of the dissolution profiles and a successful in vivo study on the highest strength. Similarly, it is also possible to get a waiver for a higher strength that is proportionally similar, if the following 3 conditions are satisfied: **1)** clinical safety and efficacy data exist for this higher dose, **2)** the drug exhibits linear pharmacokinetic characteristics over the therapeutic dose range, and **3)** comparability of the dissolution profiles among the different strengths.

  We acknowledge your submission dated July 8, 2010, requesting a BA/BE waiver for INCB018424 phosphate 10 mg, 15 mg, 20 mg and 25 mg higher strengths tablets. The preliminary review of this submission indicates that a biowaiver is appropriate for your product; however, the final recommendation will be made under the NDA. Please include in your NDA submission the biowaiver request for the 10, 15, 20, and 25 mg tablets and the supportive information described above.

Discussion:

The Sponsor asked whether following the ICH A6A decision tree is acceptable. With respect to the dissolution acceptance criteria, the Sponsor also asked whether to (b) (4) the acceptance criterion at 30 minutes to Q = or to pick a time point where a specification of Q = dissolution.

The Agency requested that this inquiry should be formally submitted for review and comment from the ONDQA Biopharmaceutics Team.

Administration using a Nasogastric (NG) Tube
Question 5:

For patients who have difficulty swallowing solids, INCB018424 phosphate tablets can be dispersed in water and administered through a nasogastric (NG) tube. The proposed study protocol to evaluate the in-use stability of the INCB018424 phosphate tablet aqueous

suspensions is provided in Attachment 3. Does the Division agree that the proposed study protocol is adequate to establish the in-use stability to support the preparation, storage and administration of the drug product suspension through a NG tube?

Agency Response:

Your proposal appears reasonable provided that the in-use study replicates the administration procedure that occurs in clinical practice and is conducted as described in the proposed labeling. In your NDA, include analytical test methods for in-use stability study, detailed procedure description of tablet suspension preparation, and data from compatibility studies with NG tubes.

Additional Comment:

Because crushing and dissolving the tablet prior to administration results in a new formulation (disperse solution/suspension) that could change the rate and extent of drug absorption, you will need to conduct a bioequivalence study comparing the disperse solution/suspension product to the intact tablet using the highest 25 mg strength tablets. Please provide your BE study protocol for review and concurrence by the Agency.

Discussion:

The Sponsor affirmed that the formulation of the aqueous suspension for administration through an NG tube is the same as the tablet since the same inert excipients are present. Since the drug product has already been considered as a BCS class 1, the Sponsor would like to submit a biowaiver for the NG tube formulation instead of bioequivalence data. The Agency stated that this request should be formally submitted for review and comment from the ONDQA Biopharmaceutics Team.

10.2.3. Drug Product Stability Study Protocol
Question 6:

The INCB018424 phosphate immediate release tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths are (b) (4) ***Tablets of the five strengths are packaged in the same container/closure system, ie, 60 counts in 75 cc HDPE bottles. A bracketing stability study protocol for the drug product is described in Drug Product, Section 8, Stability (Attachment 2). Since the stability of the tablets of the intermediate strengths is represented by the stability of the extreme strengths, the shelf-life under the recommended long-term storage conditions of the tablets of 10 mg, 15 mg, and 20 mg strength is established based on the data obtained from testing of three batches of the 5 mg and 25 mg strength tablets stored under similar conditions. The bracketing stability study protocol was submitted to the Division in a request for a Special Protocol Assessment (IND No. 77,456 SN 0084, dated March 5, 2009). In the Division's correspondence dated March 24, 2009, you have advised us that the proposed stability study protocol does not qualify for special protocol assessment because "it is covered in ICH Q1D, Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products". Does the Agency agree that the proposed bracketing protocol is acceptable?***

Agency Response:

Your approach appears reasonable. In your NDA submission, provide a detailed scientific justification for your current proposed bracketing protocol with comparative calculations for the factors could impact stability (e.g. surface areas/tablet weight or surface areas/tablet volume of each strength, and the head space in each bottle, etc.), to demonstrate that the stability of any intermediate levels is represented by the stability of these two extremes tested. If such justification can not be established, you need to modify the proposed bracketing protocol (such as including additional tablet strength(s) as needed) with justification, to ensure that the stability of each of the five strengths of drug product is represented by the stability of the proposed strengths for testing.

Discussion: **None.**

Question 7:

Incyte intends to request a Priority Review for this NDA, as the drug is being developed for an unmet medical need to treat myelofibrosis. If a Priority Review is granted for this application, the stability update (long term data at the 18-month time point) will be submitted during the review cycle (at least 30 days before the PDUFA due date). Does the Division agree that the proposed timeline for the submission of stability update is acceptable?

Agency Response:

No. Per the *Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products* (GRMPs), all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Any information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow. International Conference on Harmonization (ICH) Q1A (R2) states "long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission". While ICH Q1E: Evaluation of Stability Data, allows for the use of extrapolation to extend the shelf life beyond the available real-time long term data, it does not negate the recommended 12 months of long term data cited in ICH Q1A(R2).

Discussion: **None**

2.3. REGULATORY

Drug Product Sections 3.2.P and 2.3.P
Question 8:

INCB018424 phosphate immediate release tablets will be marketed in 5 mg, 10 mg, 15 mg, 20 mg and 25 mg strengths. For lifecycling purposes, Incyte plans to file separate documents for each of the strengths. For example, under 3.2.P.1 there will be five documents. Does the Division agree with the proposed format?

Agency Response:

Yes, however, it is preferable to include information on each strength in a single document. Data for all strengths in a tabular format will facilitate the review of your application.

Discussion: **None**

Submission of Supporting Documentation
Question 9:

Analytical methods, their validation reports, Certificates of Analysis (CoAs), process validation protocols and/or reports and literature references will be provided. The narrative text will contain hyperlinks to these respective documents. Study reports (e.g., analytical method development reports and process development reports) in electronic form will be submitted for review upon request. Does the Division agree with the proposed plan?

Agency Response:

No. Development report(s) should be included in the Pharmaceutical Development section.

Discussion:
The Sponsor stated that these summary development reports can be many pages long and asked whether these should be submitted in the summary section of the NDA or submitted within the quality section of the Application. The Agency recommended that the summary reports be submitted in section 3.2.S.2.6 Manufacturing Process Development.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were identified.

4.0 ACTION ITEMS

The Sponsor will submit and amendment to the IND to include a submission proposal for drug substance and drug product synthesized by both the [redacted]. Information to be submitted should include the availability of data requested and what will be submitted by NDA filing and in possible NDA amendments. Biopharmaceutical questions and supportive data should also be submitted in this IND amendment. The Agency committed to review this proposal as expeditiously as feasible before NDA filing.

5.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were provided for this meeting.

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

/s/

SARAH P MIKSINSKI
12/20/2010

MEETING MINUTES

MEETING/TELECON DATE: November 3, 2010 **TIME:** 3 pm – 4 pm
LOCATION: FDA, White Oak Building 22, Conference Room 1313

IND: 077456

Meeting Request Submission Date: July 15, 2010
FDA Response Date: August 1, 2010
Briefing Document Submission Date: October 1, 2010

DRUG: INCB018424 Phosphate

SPONSOR/APPLICANT: Incyte Corporation

TYPE of MEETING: Pre-NDA meeting to discuss the content and format of the planned NDA submission for treatment of myelofibrosis.

FDA PARTICIPANTS:
Ann T. Farrell, M.D., Acting Director, DHP
Edvardas Kaminskas, M.D., Acting Deputy Director, DHP
Albert Deisseroth, M.D., Medical Officer, DHP
Ashkan Emadi, M.D., Medical Officer, DHP
R. Angelo De Claro, M.D., Medical Officer, DHP
Robert Kane, M.D., Acting Deputy Director, Safety, DHP
S. Leigh Verbois, Ph.D., Supervisory Pharmacologist
Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer, DCP5
Hong (Laura) Lu, Ph.D., Biostatitics Reviewer
Alberta Davis-Warren, B.S., Regulatory Health Project Manager

INDUSTRY PARTICIPANTS:
Ron C. Falcone, Ph.D., Vice President, Regulatory Affairs
Richard Levy, M.D., Exec. Vice Pres., Chief Drug Development and Medical Officer
Adam Boyd, Ph.D., Program Statistician, Novartis Pharma AG
Susan Erickson-Viitanen, Ph.D., Exec. Director, Clinical Research Scientist
Donna Gillian-Brown, M.S., Sr. Director, Medical Writing
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William V. Williams, M.D., Vice President, Exploratory Development
Neil Wummer, Exec. Director, Regulatory Affairs
Swamy Yeleswaram, PhD, Vice President, Drug Metabolism and Biopharmaceutics

BACKGROUND: Sponsor is using INCB018424 phosphate to investigate the treatment of myeloproliferative neoplasms, hematologic malignancies and solid tumors. On July 15, 2010 Incyte Corporation submitted a meeting request to discuss the content and format of the planned electronic common technical document NDA. The proposed indication for this NDA submission is myelofibrosis. The Sponsor submitted a subsequent background package on October 1, 2010. To facilitate the meeting FDA sent preliminary responses by email on October 28, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1:

Does the Division agree with the content and format of the planned eCTD NDA for INCB018424 as described in Attachment A: Planned Contents INCB018424 eCTD NDA?

FDA Response:

We agree with the following caveats:

- **It is unclear from the Sponsor's planned eCTD nomenclature if the biopharmaceutics (2.7.1) and clinical pharmacology (2.7.2) sections will be a mere summary of studies or a comprehensive review across studies. These reports should contain both a summary of individual studies as well as a comprehensive review across studies and populations identifying clinically relevant trends and parameters regarding the PK, PD, exposure/response/ safety, and an evaluation of the effects of covariates such as age, weight, gender, race, etc. on the PK (pharmacokinetics) of INCB018424.**

- **In the appropriate clinical pharmacology and biopharmaceutics sections of the eCTD provide a table listing of patients with renal or hepatic impairment who have received INCB018424 organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation, AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

Meeting Discussion: The Sponsor will provide a comprehensive review across studies as requested above. In the table listing of patients with hepatic impairment, the Sponsor will use the NCI organ dysfunction working group criteria for hepatic impairment with the main parameter of stratification of total bilirubin.

Question 2:

Does the Division agree with Incyte's proposal, as detailed in the applicant position, to fulfill the requirements of 21 CFR 314.50(d)(5)(v) and (vi) calling for an Integrated Summary of

Effectiveness (ISE) and Integrated Summary of Safety (ISS) through the written Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) provided in CTD Module 2 with appropriate appendices located in Module 5?

FDA Response: No.

Meeting Discussion: The Sponsor and the Agency discussed the guidance for industry on integrated summaries of effectiveness and safety. A consensus was reached that would provide for detailed not comprehensive summaries of the efficacy and safety n module 2 and in module 5 complete reports for every clinical trial important for the analysis of the NDA, as well as an exhaustive and complete analyses of all the trials relevant to the discussion of efficacy and safety for INCB18424.

Question 3:

Does the Division agree with Incyte's plan to provide raw data and analysis datasets, with corresponding define files, for the studies as described below?

- Incyte plans to provide raw and analysis datasets, formatted as traditional datasets in accordance with the FDA's Draft Guidance document titled, "*Providing Regulatory Submissions in Electronic Format – General Considerations*" October 2003, for the clinical pharmacology studies INCB 18424-131, -132, -133, -134, -135, -136, -137, -138, -139, -142; Study -231 in patients with rheumatoid arthritis; Study -254 in patients with prostate cancer; and Study -255 in patients with relapsed or refractory multiple myeloma.

FDA response: Agree. However, please see our response to Question 10 for additional clarification.

- Data from Study INCB 18424-138, the Thorough QT study, will also be converted and provided as Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) raw data and analysis datasets as per the request of FDA. Data from Studies -254 and -255 will also be converted and provided as CDISC compliant SDTM for pooling with safety data from other Phase 2 and 3 studies.

- Incyte plans to provide only CDISC compliant SDTM raw data and analysis datasets for studies INCB 18424-251, -256, -351 and -352, as well as CDISC compliant integrated databases and analysis datasets for the SCS and SCE.

FDA Response: Yes

Question 4:

Does the Division agree with Incyte's plan to provide the statistical programs (SAS code) for the primary analyses, and select secondary analyses listed in the Applicant position, from Studies INCB 18424-138, -351 and -352, as both ASCII files and as Adobe pdf documents? Incyte does

not plan to provide the programs for the Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE).

FDA Response: Yes

Question 5:

Does the Division agree with Incyte's plan to provide the Case Report Forms (CRFs) as required in 21 CFR 314.50, and to also include CRFs from subjects who experienced a serious adverse event while enrolled in Studies INCB 18424-251, -256, -351 and -352?

FDA Response: Yes.

Question 6:

Does the Division agree that a table of the very common adverse reactions and clinically relevant laboratory findings from the placebo-controlled INCB 18424-351 study (Study 1) and a table of the very common adverse reactions and clinically relevant laboratory findings from the comparative study to best available therapy INCB 18424-352 study (Study 2) are appropriate to include in the labeling to present the safety profile in the myelofibrosis patient population?

FDA Response: Yes, as long as a full and complete clinical study report for each of the studies listed above is included in the NDA.

Question 7:

Incyte, in partnership with Novartis, is developing a global Risk Management Plan (RMP) for INCB018424 for the treatment of MF. Pending data analyses at the conclusion of the ongoing Phase 3 trials, further review/analyses will be conducted and the safety information will be updated as warranted. These data will be integrated into the global RMP which is planned for inclusion in Module 1.16 of the NDA. Based on a review of the current safety profile, we believe that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary as the known toxicities can be managed with product labeling, patient information instructions and a robust pharmacovigilence plan. This assessment will be revisited when the full, unblinded safety database has been reviewed. Incyte would appreciate the Division's guidance regarding whether a REMS might be required?

FDA Response: It is premature to comment on whether a REMS might be required prior to the completion of a full review of the NDA.

Question 8:

Does the Division agree with Incyte's plan to provide financial disclosure statements only for Study INCB 18424-251 A Phase 1/2 Open-Label Study in patients with PMF and Post-PV/ET MF, and the Phase 3 Studies INCB 18424-351 and -352 in patients with PMF, PPV-MF, or PET-MF?

FDA Response: Financial disclosure statements should be provided for each of the trials which are used to support the NDA and from which labeling information could be taken.

Question 9:

Does the Division agree with Incyte's proposal to include electronic datasets, consistent with the CDISC SEND standards, from only the 6 month Tg.rasH2 mice carcinogenicity study?

FDA Response: Although the agency indicated it was only necessary to submit the mouse study in 2008 at the time of NDA submission, additional guidance has been published describing oncology indications (ICH S9). It is now clear that the patient population in the proposed NDA is limited to a non-oncology patient population, and that ICH S9 is not applicable. Given the proposed patient population, the submission of the rat carcinogenicity study is also necessary at the time of NDA submission. Please see ICH S1A for additional information.

Meeting Discussion: After consideration the Agency indicated that given the refractory nature of patient population the rat carcinogenicity data would not be necessary at the time of filing but would likely be a post marketing requirement.

Question 10:

Does the Division agree with the proposed formats of the pharmacokinetic and pharmacodynamic data?

FDA Response:

We agree with the following caveats:

- **Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**
- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.**
- **We encourage you use the following submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm) when submitting pharmacometric data and models. For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation**

model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Question 11:

Does the Division agree with Inycte's plan to include information from Studies INCB 18424-251 and -351 in the Population PK report provided in the NDA submission? Does the Division agree with Incyte's proposal to provide an expanded Population PK report, which will also include data from Study -352,

FDA Response:

We agree to including information from studies INCB 18424-251, -351, and -352 in the population PK analysis. However, we do not agree with the timelines. The final population PK report and exposure-response analyses for efficacy and safety endpoints should be included in the NDA submission. The corresponding data sets and statistical programs should be submitted as described in our response to Question 10.

Meeting Discussion: The Sponsor will provide the population PK analysis report at the time of NDA submission with studies 251 and 351 in the main dataset and study 352 as validation data.

Question 12:

Does the Division agree with Incyte's proposal that all efficacy analyses will be displayed in the SCE side by side without pooling the data together based on the design differences (eg, double blind vs. open label; placebo controlled vs. active comparator) between studies INCB 18424-351 and -352?

FDA Response: Yes, as long as a unique patient identifier number is assigned to each patient so that patients from different trials can be distinguished.

Question 13:

Does the Division agree with the proposed statistical analysis plan for the SCE presentation of duration of maintenance of a ≥ 35% reduction from Baseline in spleen volume in Studies INCB 18424 -351 and -352?

FDA Response Yes.

Question 14:

Does the Division agree with Incyte's proposal not to include a meta-analysis of the survival data from INCB 18424-351 and INCB 18424-352 because of differences in the trial designs and patient populations?

FDA Response: Yes.

Question 15:

Does the Division wish to have the MRI/CT images of the spleen from Studies INCB 18424-251, -351 and -352 provided as a review-aid by [redacted] (b) (4)? If yes, does the Division prefer to be able to review the images using the Timepoint Patient Browser or the Image Query Tool?

FDA Response: No. The Division does not review MRI or CAT scans, but depends on the attributions of the Independent Review Committee (IRC). Please submit the tabulated results of the reviews of the IRC for every patient along with a tabulated summary of the IRC results along with the Charters of the IRC in your upcoming NDA. Please ensure that the identifiers in this report of the IRC are the same as the unique identifying numbers used for each patient throughout the NDA.

Question 16:

Does the Division agree with the proposal to integrate the safety data per the following three separate datasets?

1. Studies with myelofibrosis patients in randomized studies receiving the proposed labeled dose: Studies INCB 18424-351 and -352 (not including data from patients who cross over from placebo or Best Available Therapy to INCB018424).

2. Studies with myelofibrosis patients receiving all doses and regimens: Studies INCB 18424-351 and -352 (including patients who cross over from placebo or Best Available Therapy to INCB018424), and -251.

3. Studies with hematological disorders or other oncology indications including patients receiving all doses and regimens: Studies INCB 18424-351, -352, -251, -256, -254, and -255.

FDA Response: Please submit with the NDA the following separate data sets: the data sets listed in option 1, and the data sets listed in option 2. In addition, submit the data sets listed in option 3. Please integrate the safety data sets described in option 2 above into a single data set. Remember to use identifying numbers for each patient that are uniform for each patient throughout the NDA.

Meeting Discussion: A consensus was reached regarding datasets for safety. Specifically individual datasets would be provided for each study as far as for efficacy and safety, in

addition a pooled data set of safety would be provided for those studies listed under option 2; 351, 352, 251. A flagging system would be used to identify those patients in the integrated safety datasets for whom crossover had occurred.

Question 17:

Does the Division have any specific comments on the draft SCS & RMP Report Analysis Plan as detailed in the Applicant Position and in Attachment J provided with this briefing package?

FDA Response: No.

Question 18:

Does the Division agree with Incyte's plan to submit ECG datasets from all studies, including all individual ECG intervals, interpretations and comments, with the clinical study reports? ECG waveforms will be submitted to the ECG warehouse only from Study INCB 18424-138, the thorough QT study.

FDA Response: Please submit data sets and waveforms only for the TQT study and just reports from the other studies.

Question 19:

Does the Division agree with the safety data that Incyte plans to provide in the NDA for the two investigator-initiated studies?

FDA Response: Yes

Question 20:

Incyte will include the clinical study reports, including the required case report forms, from (b) (4) [redacted], but does not plan to include the raw or analyses datasets from these studies. Does the Division agree?

FDA Response: Yes

Question 21:

Does the Division agree with Incyte's plan for information to be included in the 4-month safety update?

FDA response: Yes

Question 22:

In the event that INCB018424 would need to be referred to an FDA Oncology Drugs Advisory Committee (ODAC), would the Division consider meeting with Incyte prior to any planned

Advisory Committee meeting to discuss the clinical study results and any other issues in order for a mutual understanding between both parties prior to an ODAC meeting?

FDA response: Yes

Additional comments from Statistics:

1. **Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every new value that will be appearing in the label.**
2. **For efficacy and safety analysis datasets, you are encouraged to follow the practice noted in the *Study Data Specifications*, (http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf).**
3. **To facilitate the review process, efficacy information including patient disposition, demographics, and derived primary and secondary endpoints should be included in one analysis dataset for each study unless the data structures are not compatible due to the nature of the endpoints, e.g., one record per patient type of endpoint vs. multiple records per patient type of endpoint.**

OTHER FDA COMMENTS:

REGULATORY

1. **NDA/sNDA Presentations to CDER's Division of Oncology**

   The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

   These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

   Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at http://www.fda.gov/oc/guidance/financialdis.html.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Meeting Discussion: Sponsor has orphan drug status.

4. PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Meeting discussion: The Sponsor mentioned an ongoing pediatric study being conducted by COG. The Agency suggested the Sponsor submit this protocol for review.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-#1 Mo.		>1 Mo.-# 2Year		>2-#12	
	12-16		17-64		65	
Race:	White		Black		Asian	
	Other					

6. QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

7. Office of Surveillance and Epidemiology (OSE)

- **If the Sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**

- **For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**

Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: http://www.fda.gov/cder/guidance/6359OCC.htm

- **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**

- **The Sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

8. Please complete the following table for Study X and submit this with your NDA.

Site Address Point of Contact	# Enrolled	Efficacy Measure	# Gr 3-4 AEs	# Major Protocol Violations

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

/s/

EDVARDAS KAMINSKAS
12/01/2010