

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215309Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 77101

MEETING MINUTES

Incyte Corporation
Attention: Beverly K. Folmer, MS
Associate Director, Global Regulatory Affairs CMC
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Ms. Folmer:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ruxolitinib (INCB018424) cream.

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2020. The purpose of the meeting was to obtain feedback and agreement with FDA regarding CMC aspects of ruxolitinib cream in support of an anticipated NDA filing in 4Q 2020.

If you have any questions, call Melinda Bauerlien, Senior Regulatory Business Process Manager, at 30-796-0906.

Sincerely,

{See appended electronic signature page}

Hamid Shafiei, Ph.D.
CMC Team Lead
Division of Dermal and Dental Products
Office of New Drug Product
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Date: June 10, 2020
Time: 11:00 AM
Location: Teleconference

Application Number: IND 77101
Product Name: ruxolitinib (INCB018424) cream

Indication: For topical treatment of atopic dermatitis in patients 12 years of age and older.

Sponsor/Applicant Name: Incyte Corporation

FDA ATTENDEES

Tapash Ghosh, Ph.D., Biopharm Team Lead, Office of New Drug Products
Dacie Bridge, Ph.D., Product Quality Microbiology Reviewer, Office of Pharmaceutical Manufacturing Assessment
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, Office of Program and Regulatory Operations

SPONSOR ATTENDEES

Greg Taylor, Vice President, Regulatory Affairs
Beverly Folme, Associate Director, Regulatory Affairs CMC
Gopi Vudathala, Executive Director, Regulatory Affairs CMC
Scot Hughes, Senior Director, Chemical & Process Engineer
Bhavnish Parikh, Vice President, Pharmaceutical Development
Trupti Sheth, Senior Director, Pharmaceutical Development
Jennifer Llewelyn, Senior Director, Analytical Development

1.0 BACKGROUND

The Initial IND submission was on 2/21/07. Type B End-of-Phase 2 (CMC) meeting held on January 15, 2019 to discuss the CMC development plan.

The purpose of the meeting is to obtain feedback and agreement with FDA regarding CMC aspects of ruxolitinib cream in support of an anticipated NDA filing in 4Q 2020.

2.0 DISCUSSION

Question 1:

For this non-NME NDA for ruxolitinib cream, Incyte proposes to cross-reference all Module 3 drug substance information to the drug substance section of NDA 202,192 for

Jakafi® (ruxolitinib) Tablets. Does the Division agree that cross referencing of Module 3.2.S is appropriate, and that our proposed operational approach is acceptable?

Agency Response:

From the API standpoint, it is reasonable to cross-reference all Module 3 drug substance information to the drug substance section of NDA 202,192 for Jakafi® (ruxolitinib) Tablets. The agency agrees that cross referencing of Module 3.2.S is appropriate, and that your proposed operational approach is reasonable.

Question 2:

To meet the increased demand for ruxolitinib phosphate drug substance expected with the approval of the ruxolitinib cream NDA, Incyte is (b) (4)

(b) (4)

(b) (4) Does the Division support the proposed strategy?

Agency Response:

The proposed strategy appears to be reasonable.

Question 3:

Does the Division agree that the proposed specification for the drug product is suitable and adequate for control of ruxolitinib cream for commercialization?

Agency Response:

We recommend that you add testing and acceptance criteria for the elemental impurities to the drug product release specification. If the elemental impurities are controlled by the drug substance specification, you should provide a risk-based assessment for potential elemental impurities content in the drug product to omit testing for elemental impurities. We also strongly recommend that for globule size testing to propose acceptance criteria minimally for both D50 and D90. The proposed acceptance criteria should be based on the results from pivotal clinical and registration drug product batches. Additionally, we recommend that you include testing for pH at release and at the of shelf-life and testing for weight loss at the end of shelf-life.

Although your proposed drug product testing and acceptance criteria for microbial limits (NMT (b) (4) CFU/g for TAMC, NMT (b) (4) CFU/g for TCYM, and *P. aeruginosa* and *S. aureus*: absent) as per USP <61> and USP <62> appear reasonable, non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product

during storage. For a review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43. In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
2. Include a release and stability specification for the absence of BCC in the drug product. Reference is made to USP <60> Microbiological Examination Of Nonsterile Products—Tests For *Burkholderia Cepacia* Complex; however, suitably validated alternative methods are also acceptable.

Furthermore, we have noted that you have been testing the registration batches for IVRT but you did not include IVRT acceptance criterion in the commercial drug product specification. You have also mentioned IVRT acceptance criterion of "Report results" on Page 40. We recommend that you add testing with a numeric acceptance criterion for IVRT to the commercial drug product specification. The acceptance criterion should be based on the results from the registration and pivotal clinical batches of drug product.

(b) (4)

Nevertheless, you have only submitted your IVRT method development description. Provide full IVRT method development and validation report to justify your selections of membrane/reception solution composition and other parameters including discriminating ability of the method towards critical material attributes (CMAs), critical process parameters (CPPs) and critical formulation variables in your future submission. Provide justification for the sample preparation procedures for your proposed IVRT method

(b)
(4)

Meeting Discussion:

The following comments are provided related to tests and acceptance criteria recommended for consideration for inclusion in the commercial ruxolitinib cream drug product specification.

Elemental Impurities

As elemental impurities in ruxolitinib phosphate are controlled by the drug substance specification, Incyte will perform a risk assessment to determine if additional control in the drug product specification is warranted. Based on the risk assessment, Incyte will include the test in the proposed commercial drug product specification or will provide justification for its omission in the NDA submission.

(b) (4) Size

Incyte accepts the recommendation of the Division and intends to propose numeric acceptance criteria minimally for D50 and D90 values in the NDA submission. The proposed acceptance criteria will be based on available data at the time of submission.

pH and Weight Loss

Incyte accepts the recommendation of the Division and intends to include tests of pH and Weight Loss in the proposed commercial specification. The tests will be conducted at release and at the end of the proposed shelf life.

Burkholderia cepacia complex (BCC)

Incyte accepts the recommendation of the Division and intends to include confirmation of absence of BCC in the drug product specification for release and stability testing.

IVRT

Incyte agrees with the position of the Division that IVRT is a useful tool for demonstrating “sameness” of a semisolid dosage form, and for assessing the comparability of drug product made subsequent to a manufacturing change to that made prior to the change, as discussed in the SUPAC-SS guidance document. For this reason, Incyte has developed a robust and discriminating analytical method to determine IVRT. The method is fully validated in accordance with ICH Q2(R1) and is suitable for its intended use. Detailed information regarding method development and validation, along with full description of the method parameters, will be included in the NDA. As recommended, information will be presented in the submission to justify selections of membrane/reception solution composition as well as other method parameters, and to demonstrate the discriminating nature of the method.

(b) (4)

In developing the specification for ruxolitinib cream, Incyte has considered the critical quality attributes of the drug product and has included in the specification those tests considered necessary to ensure that the drug product released for clinical and commercial use meets the requisite quality to ensure the identity, strength, quality, purity, and potency required for safe and effective use. It is Incyte’s position that the proposed tests and acceptance criteria of the

specification, with the additions discussed above, are sufficient in ensuring the quality of the drug product. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Question 4:

As part of the EOP2 briefing package, Incyte presented a proposed protocol for stability testing of registration batches of ruxolitinib cream drug product. Upon further consideration, we propose a modification to the tests performed on stability samples. Does the Division agree to the proposed modification of the stability protocol for registration stability batches?

Agency Response:

We recommend that you include testing at 24-month time-point in the long-term stability protocol for the registration batches of drug product. We have noted that antimicrobial effectiveness testing (AET) has been removed from the stability protocol for the registration batches. We recommend that you perform AET according to USP<51> or equivalent methodology on at least one primary stability batch of the drug product at the end of the proposed shelf life. We also recommended that your NDA should include data from AET performed using products formulated (b) (4) at/or below the minimum specification at release or shelf-life, whichever is lower.

Meeting Discussion:

Incyte agrees to include a 24-month time point to the long-term stability protocol as requested. We also agree to perform AET testing on at least one primary stability batch of the drug product at the end of the proposed shelf life, and to include data from AET performed on drug product (b) (4)

Question 5:

To meet expected commercial demand for ruxolitinib cream, process performance

qualification (PPQ)/commercial batches of ruxolitinib cream are planned to be manufactured at approximately (b) (4) the scale of the registration stability batches. Does the Division agree that the batch analysis and stability data on registration batches will support commercial manufacture at the increased batch size?

Agency Response:

The (b) (4) scale up for PPQ and commercial batches from the registration batches is reasonable. However, comparability of the equipment capability to manufacture quality product between scales, critical process parameters and quality of intermediate product attributes should be established, in addition to comparability of batch analysis data. Controls on critical intermediate drug product attributes, which are predictive of product quality at release and shelf life, should be established. For further details, please refer to FDA's "Guidance for Industry - Process Validation: General Principles and Practices".

Question 6:

Does the Division agree with our proposed stability commitment for first commercial and annual stability drug product batches?

Agency Response:

Your proposed post-approval stability protocol appears reasonable. However, we recommend that you add testing at the 6-month time-point to your annual stability protocol.

Meeting Discussion

Incyte agrees to include the requested 6 month time point to the annual stability protocol.

Question 7:

Does the Division agree with the proposed content plan for the ruxolitinib cream NDA, including the provision of updated stability data within (b) (4) calendar days following NDA submission?

Agency Response:

You should provide any additional stability data that you intend for the Agency to use in the determination of drug product expiration dating period with 30 days from the submission of your application. The acceptability of the content of your NDA will be evaluated during the Agency's filing review.

Meeting Discussion:

Incyte will submit any additional drug product stability data within 30 days of initial NDA submission.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID R SHAFIEI
06/12/2020 12:41:03 PM



IND 077101

MEETING MINUTES

Incyte Corporation
Attention: Deb McGill, PhD
Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. McGill:¹

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

We also refer to the teleconference between representatives of your firm and the FDA on May 13, 2020. The purpose of the meeting was to discuss the development program for ruxolitinib cream.

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

If you have any questions, call Matthew White, Senior Regulatory Project Manager at 301-796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's response to the Agency's preliminary comments

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 13, 2020, 11:00 a.m. – 12:00 p.m. EDT
Meeting Location: Teleconference

Application Number: IND 077101
Product Name: Ruxolitinib cream

Proposed Indication: For topical treatment of atopic dermatitis in patients 12 years of age and older
Sponsor Name: Incyte Corporation

Regulatory Pathway: 505(b)(1)

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie G. Beitz, MD, Director, Office of Immunology and Inflammation
Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Brenda Carr, MD, Clinical Reviewer, DDD
Mohamed Alish, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology 3
Barbara Hill, PhD, Pharmacology Supervisor, DDD
Jianyong (Jerry) Wang, PhD, Pharmacology Reviewer, DDD
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDD
Kimberle P. Searcy, MPH, Regulatory Health Project Manager, DDD
Matthew E. White, Senior Regulatory Health Project Manager, DDD

SPONSOR ATTENDEES

Xuejun Chen, PhD, VP, Clinical Pharmacokinetics
Kevin Hou, PhD, Division Vice President, Biostatistics & Programming
Michael Howell, PhD, Senior Director, Translational Research
Wilson Hu, MD, MBA, Sr. Medical Director, Global Risk Management & Safety Surveillance
Michael Kuligowski, MD, PhD, MBA, Exec. Medical Director, Inflammation & Autoimmunity

Fiona Lee, MS, Associate Director, Global Regulatory Affairs
James Lee, MD, PhD, Group Vice President, Inflammation & Autoimmunity
Deb McGill, PhD, Director, Global Regulatory Affairs
Alan Roberts, PhD, Vice President, Toxicology
Dana Shuey, PhD, DABT, Vice President, Toxicology
Kang Sun, PhD, Director, Biostatistics
Greg Taylor, PharmD, Vice President, Regulatory Affairs
May Venturanza, MD, Director, Clinical Research Scientist
Sue-Ellen Wingertz, Senior Director, Development Project Management
Swamy Yeleswaram, PhD, Group Vice President, Drug Metabolism and Biopharmaceutics

1.0 BACKGROUND

Purpose of Meeting

The purpose of this meeting is to discuss the content and format of the planned NDA submission to support the use of ruxolitinib cream for topical treatment of atopic dermatitis in patients 12 years of age and older.

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the guidance FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Regulatory Correspondence History

We have had the following teleconference with you:

- 01/15/2019: Type B meeting – End of Phase 2 – CMC only
- 10/24/2018: Type B meeting – End of Phase 2
- 04/06/2018: Type C meeting – written responses only

We have sent the following correspondence:

- 02/04/2020: Advice letter
- 01/24/2020: Deny Fast Track letter
- 04/01/2019: iPSP – written response letter
- 02/26/2019: Advice letter
- 02/04/2019: Advice letter
- 10/10/2018: Advice letter
- 07/03/2018: Partial clinical hold letter
- 07/19/2017: Advice letter

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

- 07/11/2017: Remove partial clinical hold letter
- 05/01/2017: Partial clinical hold letter
- 8/04/2016: Advice letter (2)
- 09/29/2015: Advice letter
- 06/29/2015: Study may proceed letter
- 01/31/2013: IND inactivation letter
- 03/17/2011: Advice letter
- 12/16/2010: Advice letter
- 04/16/2009: Advice letter
- 12/17/2008: Carcinogenicity SPA agreement
- 06/16/2008: Advice letter

2.0 DISCUSSION

2.1. Regulatory

Question 1:

Does the Division agree with the content and format of the planned NDA to support the use of ruxolitinib cream for topical treatment of atopic dermatitis in patients 12 years of age and older?

FDA Response to Question 1:

The Agency does not agree with Modules 1.1.2, 1.1.3, 1.1.7, 1.14.1.2, and 5.3.4. Regarding Modules 1.1.2, 1.1.3 and 1.1.7, please note that additional nodes should not be created beyond what is in the eCTD structure specifications. Please follow <https://www.fda.gov/media/76444/download> for more details regarding the eCTD structure specifications. Instead, leaf titles can be used to differentiate between documents in Module 1.1.

Regarding the duplicate Module 1.14.1.2, the first, "Draft container labels (1.5%)" should be designated as Module 1.14.1.1. Regarding Module 5.3.4, "Literature References" should be designated as Module 5.4. Please follow the link provided above for more details regarding the eCTD format.

From technical perspective (and not content related), the proposed organization of the other Modules of the planned NDA is acceptable.

Question 2:

Does the Division agree with Incyte's plan to provide the Case Report Forms (CRFs) for each participant who died or did not complete the study due to an adverse event as required in 21 CFR 314.50 and to also include CRFs for participants who had a serious adverse event while enrolled in the clinical trials included in the NDA?

FDA Response to Question 2:

This is acceptable. Please also see Additional Comments.

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Question 3:

Does the Division agree that financial disclosure is required only for the proposed studies indicated below?

FDA Response to Question 3:

You plan to provide financial disclosures for investigators in the following 3 studies: pivotal Phase 3 studies, INCB 18424-303 and -304, and the maximum use trial, INCB 18424-103. This is acceptable.

Question 4:

Does the Division agree with the amended initial Pediatric Study Plan for ruxolitinib cream for topical treatment of atopic dermatitis submitted May 22, 2019 (SN0398)?

FDA Response to Question 4:

You have requested a partial waiver of assessments for the 0 to < 3 months age group from the requirements of the PREA on the grounds that studies would be impossible or highly impracticable because substantial difficulties exist in establishing a definitive diagnosis of AD in this age group. This is acceptable.

You have requested a deferral for pediatric studies in the 2 years to < 12 years age group and the 3 months to < 24 months age group until additional safety and effectiveness data have been collected. You will include pediatric assessments in the 12 to < 18 years age group in the initial NDA, which you may be submitting in December 2020. Please provide additional information regarding the “additional safety and effectiveness data” you propose to collect to support pediatric assessments in patients < 12 years of age.

For subjects 3 months to < 24 months, you propose an open-label safety and efficacy trial with ruxolitinib cream applied BID for 4 weeks with an optional 4-week extension treatment period. In our iPSP comments, we requested that you provide your plans for assessment of long-term safety in this cohort. You replied as below:

AD in infants is more acute in nature than in older age-related presentations of this condition and tends to show a prompt therapeutic response. Therefore, the proposed treatment and follow-up period should be adequate to assess safety consistent with the expected use in this population. Based on emerging data from the clinical development program, Incyte will consider further assessments to address safety.

However, “a prompt therapeutic response” to an acute episode (or flare) does not negate the potential for chronicity of AD in the youngest cohort i.e., 3 months to < 24 months. Kim et al. found that the median duration of disease persistence was 3.0 years (mean $\pm$ SE: 5.8 $\pm$ 0.03 years) for those diagnosed at 0 to 1 year of age and 8.0 years (mean $\pm$ SE: 10.5 $\pm$ 0.09 years) for those with onset of AD by 2 to 5 years of age.²

² Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): A systematic review and meta-analysis. J Am Acad Dermatol 2016;75:681-7.

Please provide your plans for assessment of long-term safety in subjects 3 months to < 24 months.

Meeting Discussion:

The Sponsor agreed to revise the iPSP to include their plans for assessment for long-term safety (follow-up through 1 year) in subjects 3 months to 24 months of age.

2.2. Chemistry, Manufacturing, and Controls

There were no Chemistry, Manufacturing and Controls (CMC) questions in the briefing package. A separate meeting to discuss the CMC aspects of the planned submission is scheduled for June 10, 2020.

2.3. Nonclinical

Question 5:

Does the Division agree that submission of the proposed dossier of nonclinical study reports is sufficient to support the proposed NDA for topical treatment of atopic dermatitis in patients 12 years of age and older?

FDA Response to Question 5:

We agree that your proposed dossier of nonclinical study reports is adequate to support the proposed NDA submission for ruxolitinib cream for the topical treatment of atopic dermatitis in patients 12 years of age and older.

Note that in order to enable us to conduct statistical review of the 2-year dermal mouse carcinogenicity study, in addition to providing the final study report, SAS tumor data set (tumor.xpt) for the carcinogenicity study should also be provided in the NDA submission. The standard format for preparing the data is provided below for your reference.

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's May 2015 guidance document titled *"Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications"*.

The tumor dataset should be prepared in the following format:

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis ^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Comments
STUDYNUM	Study number	char		³
ANIMLNUM	Animal number	char		^{1,3}
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control to highest dose group	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		^{3,4}
TUMORNAM	Tumor name	char		^{3,4}
ORGANCOD	Organ/tissue code	char		^{3,5}
ORGANNAM	Organ/tissue name	char		^{3,5}
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	⁴
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	⁴
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

¹ Each animal in the study should have at least one record even if it does not have a tumor.

² Additional variables, as appropriate, can be added to the bottom of this dataset.

³ ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

⁴ A missing value coded with a dot (.) should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD

when the organ is unusable or not examined.

⁵ Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

Meeting Discussion:

The Agency confirmed that providing the tumor data set for the dermal mouse carcinogenicity study in accordance with the FDA Study Data Specifications v2.0, July 2012, is acceptable.

2.4. Biostats/Datasets

Question 6:

Does the Division agree with Incyte's proposed pooling strategy and planned analyses of pooled efficacy data?

FDA Response to Question 6:

Your proposal to pool efficacy data from the two identically-designed Phase 3 trials for the integrated summary of efficacy (ISE) is acceptable. Note that the ISE should include discussions regarding the strength of evidence across all trials, including discussion of any difference in outcomes across trials. Therefore, we recommend that subgroup analyses be conducted for the individual trials in addition to the subgroup analyses on the pooled data. We also note that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooled data. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

Question 7:

Does the Division agree with Incyte's proposed pooling strategy and planned analyses of pooled safety data?

FDA Response to Question 7:

You propose three pools for the integrated summary of safety (ISS). Pool 1 will be integrating results across the two identically-designed Phase 3 trials. Your proposed pooling strategy and planned analyses for Pool 1 are acceptable.

Pool 2 and Pool 3 will be integrating results across studies that have different randomization ratios, patient populations, control arms, length of follow-up, etc. Therefore, for these analyses, it will be important to use an integration method for your ISS that stratifies on study rather than simple (crude) pooling. See, for example Section V of guidance for industry "*Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products.*"

Please also see Additional Comments.

Meeting Discussion:

The Agency advised the sponsor that appropriate statistical approaches for integrating safety data across different clinical trials should be considered to account for differences in trial design (treatment arms, randomization ratios, and trial durations). This particularly applies to the proposed Pool 2 and Pool 3 of the ISS. The Agency noted that differences in the trial design could mask interpretation of study findings for the adverse event tables when crude pooling is used. The sponsor is referred to the following articles for more information regarding the Simpson's paradox and reporting adverse events:

- Crowe, B., Chuang-Stein, C., Lettis, S., & Brueckner, A. (2016). *Reporting adverse drug reactions in product labels*. Therapeutic Innovation & Regulatory Science, 50(4), 455-463.
- Chuang-Stein, C., & Beltangady, M. (2011). *Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies*. Pharmaceutical Statistics, 10(1), 3-7.

The Agency also noted that inclusion of a vehicle arm in Pool 2 would provide important information accounting for the aforementioned considerations.

Question 8:

Incyte proposes to submit the clinical data in Module 5.3.5 of the eCTD according to the standards provided in Table 3. Does the Division agree with this clinical data submission strategy/plan?

FDA Response to Question 8:

From technical perspective (and not content related), the proposed plan to submit the clinical data in Module 5.3.5 is acceptable. Please note the acceptable level at which documents should be submitted and that for clinical study reports, multiple documents should be submitted. For further guidance on acceptable submission format per Module, please follow <https://www.fda.gov/media/71551/download>.

Your proposal to submit SDTM and ADaM formatted datasets for the AD trials is acceptable.

Sensitivity analyses for the handling of missing data in the Phase 3 trials include a multiple imputation method and a tipping point analysis. Complete details regarding the sensitivity analyses should be provided, including the explicit logistic regression model, the method of imputation, the number of replications and the randomization seed for the multiple imputation and the grid of response probabilities investigated for the tipping point analysis. In addition, submit the SAS code used to implement the proposed multiple imputation methods as well as the SAS code used to analyze the imputed datasets. Also, submit the SAS code to implement the tipping point analysis.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the Phase 3 trials.

- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

From a technical standpoint the proposed this clinical data submission strategy/plan in Table 3 is acceptable. However, we highly recommend submitting the Integrated summaries (ISS and ISE) in ADaM standard since the most individual studies included in ISS and ISE are submitted in ADaM standard and ADaM standard datasets can be better fit FDA current analysis tools.

Question 9:

For all studies that are in SDTM version 3.1.2, does the Division agree with Incyte's proposal to submit the TS domain (excluding other Trial Design domains such as TA, TE, TI, TV, etc.) with only the Study Start Date?

FDA Response to Question 9:

From a technical standpoint the proposal for submitting SDTM version 3.1.2 is acceptable.

2.5. Clinical Pharmacology

Question 10:

Does the Division agree with Incyte's plan to provide pharmacokinetic (PK) data?

FDA Response to Question 10:

We acknowledge that you plan to provide PK data from 4 clinical studies conducted in subjects with AD and additional PK data from the pediatric AD study and vitiligo study. The adequacy of your PK data will be a review issue at the time of your NDA submission.

Question 11:

Does the Division agree that the correlative analysis of exposure with safety parameters is adequate to characterize systemic exposure and relationship to systemic exposure, if any?

FDA Response to Question 11:

Your proposed correlative analysis appears reasonable to support filing of your NDA; however, we also recommend you include a correlative analysis for neutrophils in your NDA. Adequacy of the data will be a review issue.

Question 12:

Does the Division agree that with the data from the Maximum Use Trial (MUsT) INCB 18424-103, the systemic exposure and bioavailability from topically applied ruxolitinib cream is adequately characterized?

FDA Response to Question 12:

We acknowledge that you conducted the Maximum Use Trial. The adequacy of your MUsT data will be a review issue at the time of your NDA submission.

2.6. Clinical

Question 13:

Does the Division agree that the data from the primary analyses of the pivotal studies, INCB 18424-303 and -304, support an NDA submission for the proposed indication?

FDA Response to Question 13:

We agree.

Question 14:

Does the Division agree that the data from the primary analyses of the pivotal studies, INCB 18424-303 and -304, support Priority Review designation?

FDA Response to Question 14:

The determination of priority review of a marketing application is made after the application is filed. Please see the Guidance for Industry titled, *Expedited Programs for Serious Conditions – Drugs and Biologics*.

Question 15:

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

FDA Response to Question 15:

In the 4-month safety, you will provide information from ongoing ruxolitinib cream studies included in the NDA submission (studies INCB 18424-303, -304, and -211), from the date of the NDA data cut-off currently planned for June 2020 through October 2020, assuming the NDA is submitted in December 2020. At the time of the planned NDA submission, the safety database will include at least 600 subjects with AD treated with ruxolitinib cream for at least 6 months and 200 subjects, including approximately 40 adolescents, treated for at least 12 months. In addition, approximately 100 subjects with vitiligo will have received ruxolitinib cream for at least 12 months in the Phase 2 study

(INCB 18424-211). At the time of the 4-month safety update, all participants in the Phase 3 AD studies will have been followed for at least 12 months.

Your plans for the 4-month safety update are acceptable.

If it is determined that your NDA qualifies for a priority review, then a safety update should be submitted no later than 3 months following initial submission of the application.

Additional Comments

Please include the following in your NDA:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation. In the narratives, please include the date and study day in the discussion relating to the event(s) e.g. "The event happened on xx/yy/2020 (study day zz). Also please include how the onset of the event relates to exposure (number of doses and date of occurrence relative to most recent dose).
- Reference ranges for all laboratory values in the data listings where those laboratory values are presented.
- In the presentation of laboratory data, please "flag" all laboratory values and vital signs that are outside of the reference ranges.
- For the placebo-controlled periods of trials and in applicable pooled analyses, please include tables of incidence rates at $\geq 1\%$ by treatment group. For the maintenance and open-label extension phases, please include a table of incidence rates at $\geq 1\%$ as well as the exposure-adjusted rates (in patient-years) by treatment group. For Pool 2 and Pool 3, refer to Response to Question 7 for appropriate integration method when integrating results across studies that have different randomization ratios, patient populations, control arms, length of follow-up, etc.
- Full-text version of any referenced articles with hyperlinks to each article, as appropriate.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily

located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for June 10, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.³ In addition, you may contact the Division of Pediatric and

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁴

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable,

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁷

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁸

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
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⁷ <http://www.fda.gov/ectd>

⁸ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

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⁹ <https://www.fda.gov/media/85061/download>

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77101

MEETING MINUTES

INCYTE CORPORATION
Attention: Beverly K. Folmer
Senior Manager, Regulatory Affairs CMC
1801 Augustine Cut-Off
Wilmington, Delaware 19803

Dear Ms. Beverly K. Folmer,

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

We also refer to the telecon between representatives of your firm and the FDA on January 15, 2019. The purpose of the meeting was to discuss Incyte's CMC development plan in anticipation of a potential NDA filing for ruxolitinib cream.

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

If you have any questions, call Grace Gnall, Regulatory Business Process Manager at (301) 796-0336.

Sincerely,

{See appended electronic signature page}

Hamid Shafiei, Ph.D.
Acting CMC Lead
Office of New Drug Products
Division of New Drug Products II
Office of Pharmaceutical Quality
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
Meeting Category: End of Phase 2

Meeting Date and Time: January 15, 2019, 11:00AM – 12:00PM
Meeting Location: Teleconference

Application Number: IND 77101
Product Name: Ruxolitinib (INCB018424) cream

Indication: Treatment of patients with atopic dermatitis
Sponsor/Applicant Name: Incyte Corporation

Meeting Chair: Hamid Shafiei, Ph.D.
Meeting Recorder: Grace Gnall

FDA ATTENDEES

Hamid Shafiei, Ph.D., Acting CMC Lead, FDA/OPQ/ONDP
Brenda Carr, M.D., Medical Officer, FDA/OND/DDDP
Florence Aisida, Regulatory Business Process Manager, FDA/OPQ/OPRO
Grace Gnall, Regulatory Business Process Manager, FDA/OPQ/OPRO

SPONSOR ATTENDEES

Greg Taylor, PhD, Vice President, Regulatory Affairs
Jane Watts, MS, Executive Director, Regulatory Affairs CMC
Beverly Folmer, MS, Senior Manager, Regulatory Affairs CMC
Bhavnish Parikh, PhD, Vice President, Pharmaceutical Development
Trupti Sheth, Senior Director, Pharmaceutical Development
Bradford Mueller, PhD, Vice President, Analytical Development
Jennifer Llewelyn, PhD, Director, Analytical Development
Dana Shuey, PhD, Executive Director, Toxicology

1.0 BACKGROUND

The purpose of this meeting is to discuss suitability of ruxolitinib cream for clinical studies, and to align with FDA on expectations for further pharmaceutical development activities in support of an NDA submission.

2. DISCUSSION

Question 1: *Considering ruxolitinib cream formulation composition, excipient safety information and intended product use, does the Division agree that the current formulation is acceptable for clinical studies and commercialization?*

FDA Response to Question 1:

Yes. We consider your proposed drug product components and formulation to be acceptable for Phase 3 clinical trials and for to-be-marketed drug product.

Meeting Discussion:

The applicant accepted FDA's response, no discussion occurred.

Question 2: *Does the Division agree with or have any feedback on our plan for evaluation of the physical form and stability of ruxolitinib cream?*

FDA Response to Question 2:

We recommend that you add testing and acceptance criteria for the globule size of the cream to the drug product specification.

Meeting Discussion:

- Incyte understands FDA's recommendation to add the globule size for the cream, content uniformity, and weight loss to the drug product specification.
- FDA recommended that Incyte make efforts to develop methods and specifications for globule size for the NDA. This data is needed to understand any changes in stability. The purpose is to ensure consistent product quality. If the data indicates that the globule size is not clinically relevant, then it could be removed in post approval.
- FDA recommended a D-50 measurement. The applicant should develop the methods to describe the precision, accuracy, and reproducibility.

Question 3: *Does the Division agree with or have any feedback on our plan for evaluation of the compatibility of the container closure system with the drug product?*

FDA Response to Question 3:

Your proposed plan for testing of the container closure compatibility appears reasonable. However, we will determine the container closure compatibility with the drug product when you submit data from testing of the container closure for extractables/leachables in the NDA.

Meeting Discussion:

The applicant accepted FDA's response, no discussion occurred.

Question 4: *Does the Division agree that the proposed specification for ruxolitinib phosphate drug substance, including omission of certain tests, is suitable and adequate for use in manufacture of ruxolitinib cream?*

FDA Response to Question 4:

Based on the information in the package, the scope of the tests for the drug substance appear reasonable, including the omission of particle size testing and microbial limits. In the NDA, in addition to justification for tests performed, also provide justification for exclusion of these tests.

Meeting Discussion:

The applicant accepted FDA's response, no discussion occurred.

Question 5: *Does the Division agree that the proposed specification is suitable and adequate for control of ruxolitinib cream at the current stage of clinical development?*

FDA Response to Question 5:

No, we do not agree. You need to add the globule size for the cream, content uniformity, and weight loss to the drug product specification.

Meeting Discussion:

- Incyte understands FDA's recommendation to add the globule size for the cream, content uniformity, and weight loss to the drug product specification.
- FDA recommended that Incyte make efforts to develop methods and specifications for globule size for the NDA. This data is needed to understand any changes in stability. The purpose is to ensure consistent product quality. If the data indicates that the globule size is not clinically relevant, then it could be removed in post approval.
- FDA recommended a D-50 measurement. The applicant should develop the methods to describe the precision, accuracy, and reproducibility.

Question 6: *Does the Division agree with or have feedback regarding the proposed registration stability program, including (b) (4)?*

FDA Response to Question 6:

No, we do not agree. We recommend that you include full long-term and intermediate stability testing of minimally the smallest and largest packaging size of each lowest and highest dosage strengths in your stability protocol for the registration batches.

Meeting Discussion:

- Incyte agreed to perform full testing. Incyte was seeking clarification on what the FDA meant by full testing. FDA confirmed that full testing is understood as testing at long term conditions (36 months), intermediate conditions (12 months), and accelerated conditions (6 months).

6.0 ATTACHMENTS AND HANDOUTS

Incyte Discussion Points Related to Q2 and Q5 IND 77101

Incyte Question 2: *Does the Division agree with or have any feedback on our plan for evaluation of the physical form and stability of ruxolitinib cream?*

FDA Response to Question 2: We recommend that you add testing and acceptance criteria for the globule size of the cream to the drug product specification.

Incyte Question 5: *Does the Division agree that the proposed specification is suitable and adequate for control of ruxolitinib cream at the current stage of clinical development?*

FDA Response to Question 5: No, we do not agree. You need to add the globule size for the cream, content uniformity, and weight loss to the drug product specification.

Incyte Comment

Incyte agrees to add tests and acceptance criteria for Uniformity in Containers (as per USP <3>) and Weight Loss to the drug product specification as requested, and will apply the revised specification to future manufactured batches intended for clinical use.

It is noted that weight loss is currently tested and reported for ruxolitinib cream batches monitored on stability, and the stability profile for weight loss was summarized in Appendix C of the briefing package, however the attribute was omitted from the specification provided in Table 5. (b) (4), fill weight is tested and reported as per the specification.

Therefore, in the revised drug product specification, Incyte will include a test for fill weight (b) (4) and a test for weight loss (b) (4)

(b) (4)

(b) (4)



(b) (4)



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/s/

GRACE A GNALL
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HAMID R SHAFIEI
01/22/2019 03:18:30 PM



IND 077101

MEETING MINUTES

Incyte Corporation
Attention: Greg Taylor, PharmD
Vice President, Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. Taylor:

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

We also refer to the meeting between representatives of your firm and the FDA on October 24, 2018. The purpose of the meeting was to discuss the development program for ruxolitinib phosphate cream for topical treatment of atopic dermatitis in patients 12 years of age and older.

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

If you have any questions, call Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor's response to Agency preliminary meeting comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: October 24, 2018, 11:00 a.m. – 12:00 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Application Number: IND 077101
Product Name: ruxolitinib phosphate cream

Proposed Indication: for topical treatment of atopic dermatitis in patients 12 years of age and older
Sponsor Name: Incyte Corporation

Meeting Chair: Jill A. Lindstrom, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, Office of Drug Evaluation (ODE) III
Jill A. Lindstrom, MD, Deputy Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jianyong (Jerry) Wang, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosch, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP III
Steven Voss, MD, Clinical Reviewer, Division of Bone, Reproductive, and Urology Products (DBRUP)
Gemma Kuijpers, PhD, Pharmacology Reviewer, DBRUP
Denise Pica-Branco, PhD, Senior Regulatory Health Project Manager, Division of Pediatric and Maternal Health (DPMH)
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Michael Howell, PhD, Senior Director of Translational Research
Michael Kuligowski, MD, PhD, MBA, Executive Medical Director, Advanced Medicines Group
Richard Leff, MD, Group Vice President, Advanced Medicines Group
Robert A. Livingston, MD, MPH, Vice President, Pharmacovigilance
Edward McKeever, Executive Director, Development Project Management
Alan Roberts, PhD, Vice President, Toxicology
Dana Shuey, PhD, DABT, Executive Director, Toxicology
Kevin Hou, PhD, Vice President Biostatistics & Programming
Kang Sun, PhD, Director, Biostatistics
Greg Taylor, PharmD, Vice President, Regulatory Affairs
May Venturanza, MD, Director, Clinical Research Scientist
Swamy Yeleswaram, PhD, Group Vice President, Drug Metabolism and Biopharmaceutics
Xuejun Chen, PhD, Executive Director, Clinical Pharmacokinetics
Fiona Lee, Associate Director, Regulatory Affairs

1.0 BACKGROUND

Purpose of Meeting:

The purpose of this meeting is to discuss the development program for ruxolitinib phosphate cream for topical treatment of atopic dermatitis in patients 12 years of age and older.

Regulatory Correspondence History

We have had the following teleconference with you:

- 4/06/2018: Type C meeting – written responses only

We have sent the following correspondence:

- 10/10/2018: Advice letter
- 7/03/2018: Partial clinical hold letter
- 7/19/2017: Advice letter
- 7/11/2017: Remove partial clinical hold letter
- 5/01/2017: Partial clinical hold letter
- 8/04/2016: Advice letter (2)
- 9/29/2015: Advice letter
- 6/29/2015: Study may proceed letter
- 1/31/2013: IND inactivation letter
- 3/17/2011: Advice letter
- 12/16/2010: Advice letter
- 4/16/2009: Advice letter
- 12/17/2008: Carcinogenicity SPA agreement
- 6/16/2008: Advice letter

2.0 DISCUSSION

2.1. Nonclinical

Question 1:

Does the Division agree that the nonclinical program, summarized in Section 15.2, is adequate to support an NDA submission for ruxolitinib cream for the topical treatment of atopic dermatitis in patients 12 years of age and older?

FDA Response to Question 1:

Yes, we agree.

2.2. Clinical Pharmacology

Question 2:

Does the Division agree that the clinical pharmacology of ruxolitinib is adequately characterized and that no additional studies are needed to support product labeling?

FDA Response to Question 2:

No, we do not agree. We recommend that you complete your maximal use PK study and assess the steady state PK profile of your final to-be-marketed product, and based on this data assess the need for clinical pharmacology studies (for example, drug interaction assessment with strong CYP3A4 inhibitors). We will review the adequacy of your data when you submit your NDA.

2.3. Clinical

Question 3:

Does the Division agree with the proposed design of Phase 3 studies INCB 18424-303 and INCB 18424-304?

FDA Response to Question 3:

Subjects will be randomized (2:2:1) to treatment with ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream for 8 weeks, during the vehicle-controlled period of the study. At Week 8, all subjects who successfully complete the vehicle-controlled period, and all Week 8 assessments may participate in the long-term safety (LTS) extension treatment period, receiving treatment with ruxolitinib 0.75% or 1.5% cream BID. Subjects received either ruxolitinib 0.75% or 1.5% cream during the vehicle-controlled period will continue that treatment; subjects who received vehicle will be randomized to either ruxolitinib 0.75% or 1.5% cream BID. During this LTS period, study visits will be every 4 weeks until the end of the study (52 weeks total). During the LTS period, subjects will self-evaluate recurrence of AD and treat the active areas (not to exceed up to 20% BSA). If lesions clear between study visits, subjects will stop treatment application 3 days after clearance.

Figure 1 from Briefing Package: NCB 18424-303 and INCB 18424-304 (Phase 3 trials) Study Schema



The basic design of the vehicle-controlled period is generally acceptable. However, see the response to Question 4 (study population). See response to Question 12 regarding the LTS. Also, provide the rationale for continuation of treatment after clearance of active disease.

Question 4:

Does the Division agree with the proposed Phase 3 treatment regimens of ruxolitinib cream?

FDA Response to Question 4:

(b) (4)

However, in the proposed Phase 3 trials, both concentrations will be used in identical populations and under identical circumstances.

(b) (4)

(b) (4)

(b) (4)

Question 5:

Does the Division agree with the proposed patient population and inclusion/exclusion criteria in studies INCB 18424-303 and INCB 18424-304?

FDA Response to Question 5:

You propose [REDACTED] (b) (4)

Unless there is a safety concern, we do not recommend [REDACTED] (b) (4)

Question 6:

Does the Division agree with the primary endpoint proposed for Phase 3 of IGA Treatment Success (Investigator's Global Assessment; Treatment Success = IGA grade of ≤ 1 with ≥ 2 -grade improvement)?

FDA Response to Question 6:

We agree.

Question 7:

Does the Division agree that the alpha-controlled endpoint of proportion of participants with ≥ 4 -point improvement on the Itch NRS from baseline to Week 8 could support a labeling claim?

Does the Division agree the endpoint of proportion of participants with improvement other than 4 points on the Itch NRS from baseline to Week 8, if demonstrated to be clinically meaningful, could support a labeling claim?

FDA Response to Question 7:

Evaluating improvement of itch, where success is defined as ≥ 4 -point improvement on the Itch NRS from baseline to Week 8 is acceptable. Including the endpoint as a secondary endpoint in an appropriate multiplicity control scheme would allow the endpoint to be considered for inclusion in labeling. To support inclusion in labeling and to interpret the results, a sufficient proportion of subjects should have a baseline score ≥ 4 .

As a possible alternative labeling claim, it appears that you will explore “clinically meaningful improvement on the Itch NRS” as you believe there may be a different threshold for clinically-meaningful relief in your target population (mild-to-moderate atopic dermatitis). [REDACTED] (b) (4)

In addition, endpoints suitable for labeling need to be adequately prespecified, including the definition of response. In your briefing package you state that you intend to determine the level of clinically meaningful change using anchor-based methods on the data for your proposed Phase

¹ Andrews' Diseases of the Skin, 11th ed. Chapter 5.

3 studies and supplemented by direct patient input. It would not be appropriate to define the success criteria for the endpoint after the data have been unblinded and analyzed.

Meeting Discussion:

The Agency emphasized that explorations into alternate thresholds on the itch NRS should occur outside the context of the Phase 3 clinical trials, as there are generalizability and interpretation concerns when the same data is used to define the threshold and establish efficacy.

Question 8:

(b) (4)

FDA Response to Question 8:

(b) (4)

Question 9:

(b) (4)

FDA Response to Question 9:

(b) (4)

(b) (4)

Question 10:

Does the Division agree with the proposed statistical analysis plan for INCB 18424-303 and -304?

FDA Response to Question 10:

- With regards to the randomization, in Section 6.3 (Measures to Minimize Bias: Randomization and Blinding) the protocol states only that subjects will be centrally assigned study treatment using interactive response technology. The section describing the randomization does not mention any stratification factors. However, in Section 10.1 (Sample Size Determination), the protocol states that the randomization will be stratified by baseline IGA (2, 3) and region (North America, Other) and that baseline IGA and region will be factors in the primary analysis. Clarify the stratification factors that will be used in the randomization. Also clarify which countries you anticipate enrolling subjects in and the proportion of subjects that you expect to be enrolled in the U.S. In many studies stratification is appropriate at the center level, and consequently center-to-center variability can be incorporated into the models, rather than just regional variability.
- You proposed use of non-responder imputation as your method of handling missing data. In addition to a primary method of handling missing data, we recommend that you include at least two alternate methods of handling missing data that use alternate assumptions as sensitivity analyses. We also recommend conducting a tipping point analysis.

Question 11:

Does the Division agree with

(b) (4)

FDA Response to Question 11:

(b) (4)

See also the response to

Question 4.

Question 12:

Does the Division agree with the design of the long-term safety (LTS) extension of the pivotal studies INCB 18424-303 and INCB 18424-304?

FDA Response to Question 12:

We agree with long-term safety (LTS) extension of your Phase 3 studies (allowance for up to 52 weeks of treatment). However, enrollment into the LTS extension will require no specific IGA score or minimum %BSA (subjects may have BSA in the range of 0%-20%). Thus, poor responders to active treatment from the initial 8-week treatment period could be continued on the failed therapy into the extension period. We recommend that you incorporate criteria for rescue or withdrawal of poor responders after 8 weeks of treatment in the LTS extension. Additionally, we recommend that you develop clinical criteria for determination of eligibility for the LTS extension (or provide the rationale for having none).

Question 13:

Does the Division agree with the proposed design of the maximal use PK study?

FDA Response to Question 13:

No. We do not agree. (b) (4)

The Agency provided information including body surface area in adolescent subject to design a maximal use PK study in previous communication where we recommended a minimum body surface area involved of at least 25% in subjects 12 years of age and older. Refer to Clinical pharmacology comments in previous written response dated 04/16/2018.

We recommend that you should target sufficient number of completers within the lowest age range and you should record the amount of formulation used by each subject. We note that your proposed maximal use PK study has (b) (4) treatment period and that terminal half-life of your topical product up to (b) (4) days. Consider a longer study period to ensure your product reaches steady-state under maximal use conditions.

Additionally, for pediatric subjects, ensure that dosing continues for a sufficient duration of time to allow the potential for clinical benefit (e.g., 8 weeks). Under 21 CFR 50 subpart D, the risks of interventions or procedures that do not present a prospect of direct benefit to enrolled children must not exceed a minor increase over minimal risk (21 CFR 50.53). The potential risks posed by immunomodulatory agents generally exceed a minor increase over minimal risk, and the risk profile of ruxolitinib phosphate cream is not well characterized at this stage of development. Therefore, study of your product in children needs to present a prospect of direct benefit that is sufficient to justify the risks (21 CFR 50.52); pediatric subjects who receive ruxolitinib in your proposed studies need to receive a sufficient number of doses to provide a potential therapeutic benefit.

Meeting Discussion:

The Agency advised the sponsor to include a higher number of pediatric subjects with a sufficient number of subjects within the lowest age range. The Agency acknowledged the sponsor's modification to enroll subjects with at least 25 %BSA involvement and recommended not to have any upper limit for BSA involvement to be treated. The Agency recommended to record the total amount of product applied and the %BSA treated in each subject.

Question 14:

Does the Division agree with the proposed supportive studies to be conducted in parallel with Phase 3?

FDA Response to Question 14:

You propose the following supportive safety studies to be conducted in parallel the pivotal Phase 3 studies:

- A 6-week repeat insult patch test study in 200 (evaluable) healthy volunteers (INCB 18424-106)
- A 6-day cumulative irritation study in 30 healthy volunteers (INCB 18424-104)
- A 6-week photo-allergic patch test study in 50 healthy volunteers (INCB 18424-105)

- A 4-day photo-irritation patch test study in 30 healthy volunteers. (INCB 18424-107)

You will need to adequately characterize the local safety of your product, including irritancy and contact allergy potential, as well as photoallergic and phototoxic potential if your product absorbs UV light of relevant wavelengths. We recommend that in your clinical trials you actively assess for local site reactions using relevant scales and evaluate subjects who develop reactions suggestive of contact allergy or photosensitization using diagnostic patch and/or photopatch testing. See also ICH S10.

2.4. Regulatory

Question 15:

Does the Division agree with the proposed safety database to support an NDA submission for ruxolitinib cream for the topical treatment of atopic dermatitis in patients 12 years of age and older?

FDA Response to Question 15:

Pertaining to the AD program, you state that at the time of the planned NDA submission, “1000 (subjects) will be enrolled with approximately 600 for at least 6 months and 200 for at least 12 months.” Clarify if “enrolled” reflects the numbers of subjects exposed to study product at concentrations and under conditions intended for clinical use. You did not discuss the numbers of adolescents that you intend to include in the safety database.

The ICH E1a numbers represent a minimal number for safety. You are developing a novel product for an indication that significantly impacts the pediatric population. In light of the bone toxicity identified in the juvenile animal study, justify the size of the safety database that you propose to have at the time of NDA submission. (b) (4)

. At the time of NDA submission, the safety database should be sufficient to support the target patient population(s) and the concentration(s) intended for clinical use under intended conditions for clinical use (dosing frequency and duration).

Meeting Discussion:

The Agency encouraged the sponsor to provide a safety database of sufficient size to support the safety of their product, including information from a sufficient proportion of pediatric subjects.

Post-Meeting Addendum:

The number of subjects needed for assessing safety depends on the frequency of the expected adverse events. Consequently, it is difficult for the Agency to specify the numbers required for safety assessment. The sponsor should utilize the information they have about the adverse events of their product and plan the size of the safety database to observe expected adverse events with a good probability.

Question 16:

Does the Division agree with the proposed approach described in Section 7 to address pediatric requirements? If the Partial Clinical Hold is not resolved within 60 calendar days after the End-of-Phase 2 meeting, should Incyte still submit an initial PSP?

FDA Response to Question 16:

You plan to request a partial waiver of assessments for the pediatric age group 0 to < 3 months of age on the grounds that studies would be highly impractical because of substantial difficulties in establishing a definitive diagnosis of AD in this age group. You plan to request a deferral for pediatric studies in the age groups 3 months to < 2 years of age and 2 to 11 years of age until additional safety or effectiveness data have been collected. (b) (4)

(b) (4) agree to waiver of study of pediatric age group 0 to < 3 months of age. (b) (4)

Per the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. Please see "PREA REQUIREMENTS" in Section 3 of this document below. We recommend that you include discussion of the role of your product(s) in the armamentarium of AD treatments, if its use is ultimately precluded in a segment of the pediatric population, given the prevalence of AD in the pediatric population.

Meeting Discussion:

The Agency advised the sponsor to submit, in the iPSP, a deferral request for the study of subjects 3 months to 12 years of age and a partial waiver request for study of subjects less than 3 months of age. The sponsor should include discussion of current safety information to support the deferral request.

2.5. Follow-up to Partial Clinical Hold of 03 JUL 2018

Question 17:

Does the Division agree that the biomarkers currently under consideration would provide appropriate safety monitoring for early detection of bone effects in pediatric subjects?

FDA Response to Question 17:

Please submit your proposal and question to the IND, separate from the EOP2 meeting package.

Question 18:

Does the Division agree with the proposed amendment to INCB 18424-102?

FDA Response to Question 18:

See response to Question 17.

Question 19:

Does the Division agree, that for the intended patient population of children > 2 years of age, the animals dosed in the definitive juvenile rat toxicity study from Days 21-63 postpartum represent the most relevant age group? Further, does the Agency agree with the NOAEL defined for this cohort (b) (4)

FDA Response to Question 19:

Yes, we agree that the animals dosed in the juvenile rat toxicity study during postpartum Days (PPDs) 21 – 63 correlated with children > 2 years of age. However, we do not agree with the NOAEL of (b) (4) for this cohort. In your definitive juvenile rat toxicity study, different dose levels and endpoints were studied for different cohorts. The data suggested that younger age is more susceptible to the test article induced bone toxicity. Considering the totality of data, especially the radiography and bone densitometry findings, the NOAEL was determined to be 5 mg/kg/day for the cohort dosed during PPDs 21-63.

Question 20:

Does the Division agree with the estimate for safety margins?

FDA Response to Question 20:

No, we do not agree with the safety margin calculated based on a NOAEL of (b) (4). We calculated the safety margin based on AUC comparison, between the AUC_{0-24h} values at the NOAEL (5 mg/kg/day) in the definitive juvenile rat toxicity study (36 and 151 ng•hr/ml on PPD 63, for males and females in the cohort dosed during PPDs 21-63, respectively) and the projected human AUC_{0-24h} value provided by you (1144 nM•hr; 462 ng•hr/ml based on a molecular weight of 404). We do not calculate the safety margin based on “unbound” AUC values.

For the cohort dosed during PPDs 21-63, the safety margins were 0.1 and 0.3, for males and females, respectively.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JILL A LINDSTROM
11/20/2018