CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211488Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 211488

REFUSAL TO FILE

Camargo Pharmaceutical Services, LLC
US Agent for Foresee Pharmaceuticals Co., Ltd.
Attention: Eric Kendig, PhD
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Kendig:[1]

Please refer to your new drug application (NDA) dated March 28, 2019, received March 28, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Leuprolide Mesylate Injectable Suspension, 50 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. In an information request (IR) dated May 7, 2019, you were asked to provide test protocols and reports verifying that the combination product device constituent meets the device design requirements and specifications, including dose accuracy, break loose force, and glide force. Design verification testing on a statistically valid sample size to achieve a 95% confidence interval was requested, as well as stability testing to support the complete shelf life of the to be marketed product. Your response dated May 13, 2019 indicated that device design verification was not performed for the combination product, rather, device design requirements were verified at release and as part of the stability studies. This response is not adequate. The following information is necessary to file your submission:

    a. In some situations, it may be acceptable to substitute stability data for design verification if an appropriate sample size is tested on stability. However, submission of stability data in lieu of design verification it is not acceptable in your submission, as the provided stability data does not include an adequate sample size to demonstrate 95% confidence. Provide design verification data on the final finished combination product, including test protocols and reports, for the EPRs using an appropriate sample size to achieve a 95% confidence interval. Please be reminded that for prefilled syringes, we recommend that the EPRs include dose accuracy, break loose force, and glide force.

[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.

b. You provided summary stability data in your May 13, 2019, response document. However, stability results for injectability were provided for only two product lots. Conduct stability testing on a minimum of three product lots. Provide stability data on three product lots to show that the device essential performance requirements are met at the end of the proposed shelf life. Alternatively, provide a scientific justification that stability data on two product lots is adequate to support the shelf life.

c. The injectability specification for the proposed combination product is (b) (4) . However, the injectability data provided in Tables 2 and 4 of your May 13, 2019, response document appear to exceed the device injectability specification. Clarify whether or not the injectability data you submitted is within specification after aging. Provide stability testing to demonstrate that device EPRs are within specification at the end of the claimed shelf life. If complete real-time testing is not currently available, you may submit accelerated testing representative of the complete shelf life, as well as any real time testing currently completed. Provide stability testing to support the complete shelf life on the to be marketed product. If the device performance is outside of the device specifications (e.g., injection force), provide a root cause analysis, mitigations implemented, and evidence to demonstrate effectiveness of the mitigations.

2. Your submission has identified Foresee Pharmaceuticals as the application holder, and several facilities as involved in the manufacturing of the combination product. Identify the firm(s) responsible for designing, fabricating, assembling, labeling, packaging, holding, and storing the finished combination product.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at: OSECONSULTS@cder.fda.gov.

If you have any questions, contact Clara Lee, Regulatory Project Manager, at 240-402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/

AMNA IBRAHIM
05/23/2019 05:21:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 103206

MEETING MINUTES

Foresee Pharmaceuticals Co., Ltd.
c/o Camargo Pharmaceuticals Services, LLC
Attention: K. Gary Barnette, PhD, VP of Drug Development
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Dear Dr. Barnette:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Leuprolide Mesylate Injection Suspension (LMIS), 50 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 23, 2017. The purpose of the meeting was to discuss and gain agreement on the adequacy of the referenced clinical and nonclinical information, in combination with the completed drug development program to support the NDA, and the structure and content of the application.

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 Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug and Evaluation Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 23, 2017, 12:00pm – 1:00pm, EST
Meeting Location: White Oak Bldg. 22, Conf. Room 1419

Application Number: IND 103206
Product Name: Leuprolide Mesylate Injection Suspension (LMIS)

Indication: Advanced prostate cancer
Sponsor/Applicant Name: Foresee Pharmaceuticals, Inc.

Meeting Chair: V. Ellen Maher, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
V. Ellen Maher, MD, Clinical Team Leader, DOP1
Dow-Chung Chi, MD, Clinical Reviewer, DOP1
Todd Palmby, PhD, Nonclinical Team Leader, DHOT
Wimolnut Manheng, PhD, Nonclinical Reviewer, DHOT
Erik Bloomquist, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Reviewer, DBV
Xiao-Hong Chen, PhD, Product Quality Assessment Leader, OPQ
Danuta Gromek-Woods, PhD, Product Quality Reviewer, OPQ
Daniel Obrzut, PhD, Product Quality Reviewer, DPA3
Okpo Eradiri, PhD, Biopharmaceutical Team Leader, OPQ
Jessica Boehmer, MS, Acting Regulatory Scientist, DHP
Kim J. Robertson, Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES
Benjamin Chien, Executive Chairman, Foresee Pharmaceuticals
John Mao, Senior Vice President and Head of Development, Foresee Pharmaceuticals
Yisheng Lee, CMO, Foresee Pharmaceuticals
Yuhua Li, Vice President of R&D, Foresee Pharmaceuticals
Shih Tsung Huang, Medical Consultant, Foresee Pharmaceuticals
Grace Hu, Statistician, Consultant, Foresee Pharmaceuticals

Gary Barnette, PhD, Senior Vice President of Scientific and Regulatory Affairs
Camargo Pharmaceutical Services
Lynn Gold, Vice President of Scientific and Regulatory Affairs, Camargo Pharmaceutical Services
Wen-Yee Choi, Scientific and Regulatory Manager Camargo Pharmaceutical Services

1.0 BACKGROUND

The purpose of this meeting is to discuss an upcoming NDA submission under the 505(b)(2) pathway planned by Foresee Pharmaceuticals for Leuprolide Mesylate Injection Suspension (LMIS). LMIS is a long-acting, subcutaneous form of leuprolide administered every 6 months. This product differs from other leuprolide products in that it contains leuprolide mesylate rather than leuprolide acetate. It also contains polylactic acid and N-methyl-2-pyrrolidone. LMIS is administered by subcutaneous injection every 6 months. The Sponsor's intended indication is the palliative treatment of advanced prostate cancer.

In a Phase 3 trial, LMIS was administered on Days 0 and 168. The trial enrolled 137 patients. Testosterone levels were obtained on Day 28, every 28 days x 4, Day 168 (prior to dosing and 2, 4, and 8 hours later), Days 169, 170, and 171, and every 28 days x 6 until Day 336. The primary endpoint was the percentage of patients with testosterone <50 ng/dL between Day 28 and 336. The Kaplan-Meier method was used to assess the percentage of patients maintaining castrate testosterone levels and the 95% confidence interval.

- The Sponsor reported that 97.0% (95% CI: 92.2, 98.9) of patients maintained castrate testosterone levels between Weeks 4 and 48.

Thirty patients (30) were followed for an additional year on LMIS every 6 months.

There were 3 deaths during the treatment period due to pulmonary embolism, CVA, and progressive prostate cancer. Additionally, subdural hematoma was reported in 2 patients and myocardial infarction in 1 patient. Grade 1-4 adverse events in >5% of patients include: hot flush, hypertension, extremity pain, injection site pain, fatigue, arthralgia, nocturia, nasopharyngitis, and back pain.

FDA sent Preliminary Comments to Foresee Pharmaceuticals, Inc. on October 20, 2017.

2. DISCUSSION

1. Foresee Pharmaceuticals plans to submit an NDA for LMIS 50 mg via the 505(b)(2) regulatory pathway. In the Type C Meeting Written Responses (August 6, 2016; Reference ID: 3968886), the Division indicated that this appears to be the appropriate regulatory pathway for NDA submission. The Sponsor proposes to rely on the following information to support product approval:

    a. Clinical efficacy data from the Sponsor-conducted Phase 3 study.

b. Nonclinical and clinical safety information from Sponsor-conducted studies and information in the published literature.

c. The nonclinical safety information supporting the approval of Lupron as reflected in the approved labeling (NDA 019010; Abbvie, Inc.).

Question 1 Based on the information provided in the meeting information package, will the Agency confirm that the 505(b)(2) regulatory pathway still appears to be appropriate for submission of the LMIS 50 mg NDA?

FDA Response: A 505(b)(2) application would be an acceptable approach at this time based on the information provided.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness. Assuming that reliance on a discontinued drug is appropriate, the discontinued status of this product may pose certain challenges for you to provide an acceptable scientific bridge to the Agency's finding of safety and/or effectiveness for the listed drug.

Discussion Point: No discussions were required.

2. In Section 1.14.1.2 of this meeting package, Foresee provides annotated draft labeling that reflects the information from the approved LD labeling (Appendix 1) on which Foresee proposes to rely to support the LMIS 50 mg NDA.

Question 2 Does the Division agree that the draft labeling content is complete and appropriately referenced with the information (including information from the approved Lupron labeling) upon which Foresee plans to rely?

FDA Response: In Section 6, please format your adverse events table to provide all grade and grade 3-4 adverse events and provide the percentage of patients who developed grade 1-4 and grade 3-4 laboratory abnormalities during the study period. Please use CTCAE version 4 to grade the laboratory abnormalities. (b) (4)

Discussion Point: No discussions were required.

3. A table listing the key agreements reached between Foresee and the Division throughout the development program with regards to the proposed elements of the NDA submission is provided in **Error! Reference source not found.**.

Question 3 The Sponsor proposes that the information that will be included in the NDA is sufficient for acceptance for review. Does the Division have any suggestion on additional information that is needed for filing and/or approval of the proposed NDA?

FDA Response: Based on the information provided, the Phase 3 study may be sufficient to satisfy the requirements for review of the LMIS 50 mg NDA. However, decisions concerning filing or approval can only be made after review of the submitted data.

Discussion Point: No discussions were required.

4. The electronic NDA submission will include all tables, listings, and analysis data sets from Study FP01C-13-001 and Study FP01C-13-001-EX generated for the respective clinical study reports conforming to Clinical Data Interchange Standards Consortium (CDISC) submission standards. Case report forms and narratives for serious adverse events (SAEs), deaths, and discontinuation due to adverse events (AEs) will also be provided.

Question 4 Does the Division find Foresee's proposal for submission of efficacy and safety data acceptable for acceptance of the NDA application for review?

FDA Response: Yes. Please see response to Question 5.

Discussion Point: No discussions were required.

5. Foresee has conducted a single pivotal clinical and efficacy study (FP01C-13-001) and a safety extension of this study (FP01C-13-001-EX). Clinical information from these studies, along with supportive information from the published literature, will be summarized in Module 2 of the marketing application. As these data from the Sponsor-conducted study and the literature studies cannot be integrated, all text and in-text tables can be incorporated into Module 2, particularly Sections 2.7.1, 2.7.2, 2.7.3, and 2.7.4 of the NDA.

Question 5 Does the Agency agree that no Integrated Summary of Efficacy or Integrated Summary of Safety is required for the LMIS 50 mg NDA and that the Sponsor's plan for presenting the efficacy and safety data in Module 2 is sufficient for NDA acceptance for review?

FDA Response: Integrated Summaries of Efficacy and Safety are not required. It is acceptable to include a discussion of the adverse event and laboratory findings from FP01C-13-001 in the context of the findings (from the approved package insert) from other 6 month formulations of leuprolide in a Summary of Clinical Safety in Module 2.

Study reports from FP01C-13-001 and FP01C-13-001-EX and their associated datasets should be included in Module 5. Please include narratives, regardless of the relationship of the event to study drug, for all patients who died during the study

period, permanently discontinued study drug, or developed a serious adverse event. Please include complete case report forms for each patient for whom a narrative is submitted. We may request additional narratives or case report forms.

Discussion Point: No discussions were required.

6. Foresee plans to rely on nonclinical safety information (specifically data on carcinogenicity, mutagenicity, and impairment of fertility) from Lupron (NDA 019010; Abbvie, Inc.), as reflected in the approved Lupron labeling. Pharmacokinetic (PK) data collected in the Phase 3 study demonstrate that, following a burst phase of serum leuprolide concentrations (maximum concentration [C_{max}] of 99.7 ng/mL and 93.7 ng/mL after first and second injections; T_{max} = 3.7 hours [h]), mean serum concentrations remained relatively constant (0.37–2.97 ng/mL) from 72 h to 6 months post-injection.

   Foresee has conducted an in silico comparison of the steady-state PK parameters of LMIS 50 mg and Lupron 1 mg daily injections (Study FSEE-CSC-100; Appendix 2**Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.**). The simulation demonstrates that:

   a. The exposure to leuprolide at steady state is approximately 5 times higher from Lupron than from LMIS 50 mg (6.11 vs 1.30 ng/mL, respectively). The calculation of these values excludes the LMIS 50 mg burst phase from 0–72 h post-injection.

   b. The overall exposure (Area under the curve $[AUC]_{0\text{-}6mon;}$ mean value of 24696 ng·h/mL for Lupron 1 mg compared to 6611 ng·h/mL for LMIS 50 mg) and absolute C_{max} (mean value of 116 ng/mL for Lupron 1 mg compared to mean value of 79.5 ng/mL for LMIS 50) of leuprolide were significantly lower for LMIS 50 mg.

   Foresee proposes that the lower exposure to leuprolide from its product compared to that from the LD establishes a scientific bridge to rely on the nonclinical data in the Lupron labeling. The bridge is further supported by data from Sponsor-conducted clinical and nonclinical studies demonstrating similar safety profiles of LMIS 50 mg and other leuprolide products.

Question 6 Does the Agency agree that the comparison of pharmacokinetic data, with supportive safety data, for LMIS 50 mg and Lupron 1 mg is sufficient to support the reliance on nonclinical safety information from the LD, Lupron 1 mg labeling?

FDA Response: Yes. However, final decision will be an NDA review issue.

Discussion Point: No discussions were required.

7. Foresee proposed to conduct a single pivotal trial to fulfill the efficacy requirements of an NDA for LMIS 50 mg in the Pre-IND (12 November 2008; Pre-IND 103206 meeting minutes) and Type C (Meeting Minutes, 06 August 2016; Reference ID: 3968886)

meetings for this product. The Division agreed that a single Phase 3 trial would be potentially sufficient to satisfy clinical efficacy requirements for NDA submission. The Phase 3 trial (FP01C-13-001; NCT02234115) was completed in October 2016, with the following efficacy results:

a. Both the intent-to-treat (ITT) and per protocol (PP) populations showed that more than 98% of subjects had a serum testosterone level suppressed to castrate level (≤ 50 ng/dL) by Day 28 ± 1 (day) following the first injection of LMIS 50 mg.

b. The percentage of subjects with testosterone suppression (≤ 50 ng/dL) from Week 4 through Week 48 was 97.0% (2-sided 95% confidence interval [CI]: 92.2 - 98.9) and 97.6 (2-sided 95% CI: 92.7–99.2) of subjects in the ITT and PP populations, respectively.

c. Two of 137 subjects (1.5%) did not reach castrate levels on Day 28. One subject had a baseline level of 620 ng/dL, and his testosterone level was suppressed to 61.4 ng/dL on Day 28, and then reached castrate levels at the next measurement (Day 56) at 9.2 ng/dL. This subject stayed below 50 ng/dL for the duration of the study. The second subject had a baseline value of 365 ng/dL, and his testosterone level was suppressed to 53.4 ng/dL on Day 28 and 59.8 ng/dL on Day 56 before rebounding to 257 ng/dL on Day 84 with accompanying increasing Prostate Specific Antigen (PSA) levels, at which time he was discontinued due to lack of efficacy. Following the second injection of LMIS 50 mg, 2 subjects (2/137; 1.5%) each exhibited 1 episode of transient post-suppression breakthrough (serum testosterone >50 ng/dL). One subject showed 54.7 ng/dL on Day 170, while the other showed 61.4 ng/dL on Day 170 and 61.4 ng/dL on Day 171. Both subjects' serum testosterone levels returned to castrate levels and stayed below through the remainder of the study.

Foresee believes that these results adequately demonstrate the efficacy of LMIS 50 mg for NDA approval. These data are summarized in the annotated draft labeling (Section 1.14.1.2).

Question 7 Based on the information provided in the meeting information package, will the Agency confirm that the Sponsor's single Phase 3 study is sufficient to satisfy the efficacy requirement for acceptance for review of the LMIS 50 mg NDA?

FDA Response: Based on the information provided, the Phase 3 study may be sufficient to satisfy the efficacy requirement for review of the LMIS 50 mg NDA. However, decisions concerning filing or approval can only be made after review of the submitted data.

Discussion Point: No discussions were required.

8. At NDA submission, Foresee expects to provide a safety database consisting of the following information:

    a. Safety and tolerability information from the Sponsor's Phase 3 (n = 137 patients treated with LMIS 50 mg for up to 1 year) and the Phase 3 safety extension study (n = 30 patients treated with LMIS 50 mg for up to 1 additional year; 2 years total exposure). The most common AEs (incidence > 6%) in the Phase 3 study were hot flush, hypertension, pain in extremity, injection site pain, fatigue, and arthralgia; these are similar to the AEs associated with approved leuprolide products.

    b. An FDA Adverse Event Reporting System (FAERS) database search identifying AEs in male patients where a leuprolide product was listed as the primary suspect drug; the search will include first quarter (Q1) 2017 through the most recently available quarter to capture AEs that were not included in the most recent labeling update (May 2017) for Lupron Injection.

    c. Supportive safety data from patients with prostate cancer treated with 6-month formulations of leuprolide in published studies.

    Adverse event data will be presented in the annotated draft labeling (Section 1.14.1.2).

Question 8 Does the Agency agree that the proposed safety database is sufficient to satisfy the safety requirements for acceptance for review of the LMIS 50 mg NDA?

FDA Response: This will be a review issue. Please see the responses to Question 3 and Question 5.

Discussion Point: No discussions were required.

9. Foresee has manufactured 3 registration batches for use in the Good Laboratory Practice (GLP) toxicity and clinical studies, and has collected long-term stability data for up to 3 years on these batches (**Error! Reference source not found.**). Foresee plans to manufacture commercial product using the same process as used for the clinical study material. Based on the current projections, the target scale for this commercial program is (b) (4). The scale, critical process parameters and summary of the manufacturing process will be provided in Section **Error! Reference source not found.**.

Question 9 Does the Agency agree with the manufacturing plan for registration and commercial supply?

FDA Response: The proposed scale-up plan from the registration batch to commercial supply is acceptable. The adequacy of the manufacturing process will be a review issue.

Discussion Point: The Agency stated that the Sponsor may request an additional CMC only meeting for further discussion of CMC related matters.

10. The proposed release and stability criteria for the LMIS 50 mg commercial product will be provided in Section **Error! Reference source not found.**.

Question 10 Does the Agency agree with the proposed release and stability specifications for the commercial product?

FDA Response: Overall, the proposed drug product testing appears to be reasonable. However, you will need to established acceptance criteria for tests where currently proposed acceptance criteria are "Report results" or "For information". Please also refer to Type C "Written Responses Only" meeting minutes dated August 6, 2016, outlining the Agency's position regarding controls of your LMIS drug product. Specifically, FDA requested that you address a control strategy for particle size of leuprolide mesylate in the suspension formulation, which does not seem to be reflected in the proposed specification.

Final acceptability of the proposed specifications will be determined based on totality of data submitted in your NDA.

Regarding the setting of the in vitro drug release QC specification (as well as the FDA expectations regarding the qualification of the proposed QC drug release method), refer to the Type C (Written Response Only) Meeting Minutes provided on August 6, 2016, as well as the Clarifying Question Responses dated September 23, 2016.

Discussion Point: The Agency stated that the acceptability of the currently proposed drug release acceptance criteria will be based mainly upon the profiles of the pivotal clinical lots during use in the trial, as well as on the ability of such specification to reject unacceptable drug product batches. In the NDA, the Sponsor should also provide data regarding the discriminating power of the final proposed QC in-vitro drug release method for changes in critical quality attributes of the drug product including droplet particles size distribution and attributes of the release controlling excipients.

The data generated with respect to the discriminating power of the method for the (b) (4) ***appears to be adequate. The acceptability of the proposed specification of*** (b) (4) ***will be determined during the NDA review based upon the totality of data.***

The Agency recommends that the Sponsor generates data for batches with various sizes of droplets to determine whether it affects in-vitro drug release and drug product stability. Whether the droplet particle size will be a part of the drug product specification will be determined during the NDA review. The Sponsor will attempt to develop and validate a QC method to control droplet size if it is determined that the droplet size is a critical quality

attribute. Alternatively, the Sponsor should provide justification for not providing such a QC method.

Additional FDA Comments:

1. **In the NDA, (if available), include pH-solubility data for all known polymorphs of the API at (b) (4).**

   Discussion Point: No discussions were required.

2. **In the NDA, provide data regarding the influence of stress factors (e.g., heat, applied pressure, or exercise and fever on the in vitro and in vivo drug release profiles) of (b) (4) from the proposed drug product. If applicable, provide the IVIVC/IVIVR study report.**

   Discussion Point: The Agency corrected the drug product name as it should have read LMIS as opposed to "(b) (4)".

3. **In your NDA submission, please state the laboratory that analyzed the serum testosterone levels. Provide detailed information concerning sample handling and storage as well as the assay method and the quality control/quality assurance procedures.**

   Discussion Point: No discussions were required.

4. **Given the presence of (b) (4) in the formulation, compatibility data including extractables/leachables for all formulation contacting (b) (4) manufacturing equipment components as well as container closure system is expected as per 21CFR211.65.**

   Discussion Point: No discussions were required.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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.

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 Information* and *Pregnancy and Lactation Labeling Final Rule* 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of

such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

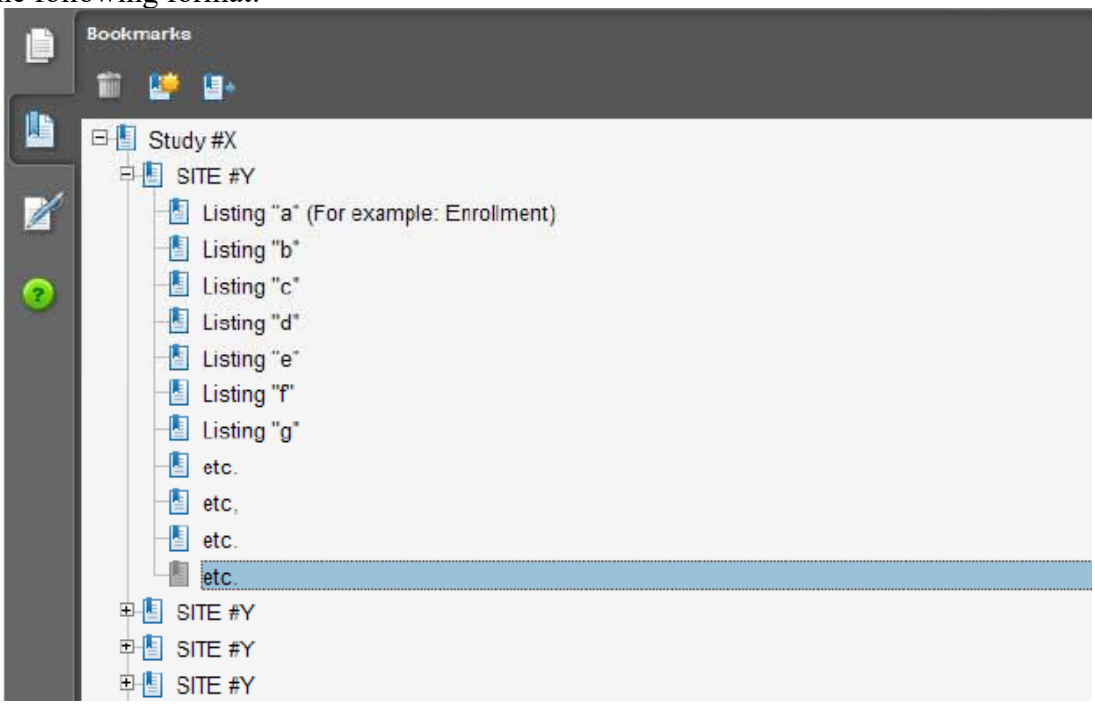
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

KIM J ROBERTSON
11/20/2017

VIRGINIA E MAHER
11/21/2017