CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214410Orig1s000
210854Orig1s004,s010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 126653
NDA 210854

MEETING PRELIMINARY COMMENTS

Genentech, Incorporated
Attention: Roberto Barrozo, PhD
Associate Regulatory Program Director
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Barrozo:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for baloxavir marboxil (S-033188) tablets.

Please also refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XOFLUZA (baloxavir marboxil) tablets.

We also refer to your correspondence, dated and received on July 24, 2019 (NDA 210854), and July 25, 2019 (IND 126653), requesting a meeting to discuss the results of the Phase 3 miniSTONE 2 study (CP40563) and the Phase 3 BLOCKSTONE study (1719T0834/XV41428), as well as the content and format for the planned Pediatric NDA and Post-Exposure Prophylaxis (PEP) sNDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

[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.

If you have any questions, call me, at (301) 796-5964 or at the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Christine Kim, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA/Pre-sNDA

Meeting Date and Time: October 10, 2019; 9:30 am – 11:00 am, EST
Meeting Location: FDA White Oak Campus, Bldg. 21, Room 1539

Application Number: IND 126653, NDA 210854
Product Name: XOFLUZA (baloxavir marboxil) tablets, 20 mg and 40 mg

Indication: Treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours
Sponsor Name: Genentech, Inc. (Genentech)

FDA ATTENDEES (tentative)

OND/OAP/Division of Antiviral Products (DAVP)

- Debra Birnkrant, MD, Director
- Jeffrey Murray, MD, MPH, Deputy Director
- Mary Singer, MD, PhD, Medical Team Leader
- Melisse Baylor, MD, Medical Officer
- Julian O'Rear, PhD, Clinical Virology Team Leader
- William Ince, PhD, Clinical Virology Reviewer
- Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Leader
- Deacqunita Diggs, PhD, Pharmacology/Toxicology Reviewer
- Karen Winestock, Chief, Project Management Staff
- Christine Kim, PharmD, Regulatory Project Manager
- Poonam Mishra, MD, Safety Deputy Director

OTS/OCP/Division of Clinical Pharmacology IV (DCP4)

- Vikram Arya, PhD, FCP, Clinical Pharmacology Team Leader
- Hassan Hazem, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)

- Erika Englund, PhD, Product Quality Team Leader
- Milton Sloan, PhD, Product Quality Reviewer

OTS/OB/Division of Biometrics IV(DBIV)

- Thamban Valappil, PhD, Statistical Team Leader
- Fraser Smith, PhD, Statistical Team Leader

SPONSOR ATTENDEES

Genentech, Inc.

- Roberto Barrozo, PhD, Associate Program Director, Regulatory
- Michael Woods, PharmD, Associate Program Director, Regulatory

F. Hoffman-La Roche

- Shiva Neysari, PhD, Global Regulatory Lead
- Barry Clinch, PhD, Global Head of Infectious Diseases
- Laura Macutkiewicz, PhD, Principal Clinical Development Scientist
- Emma Harrell, BSc, Senior Director Safety Science
- Sophie Dimonaco, MSc, Principal Statistical Scientist
- Steffen Wildum, PhD, Principal Scientist Virology
- Inaâm Bouchouika, MSc, Technical Regulatory
- Vincent Duval, PharmD, Clinical Pharmacologist

Shionogi & Co., Ltd

- Takeki Uehara, PhD, Global Project Leader, Senior Director
- Keiko Kawaguchi, MSc, Project Statistician
- Robert Ibbotson, BSc, Regulatory Affairs

Biomedical Advanced Research and Development Authority (BARDA)

- Karl Erlandson, Technical Representative
- Melissa Willens, Regulatory
- Corinna Pavetto, Clinical Operations

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 10, 2019, 9:30 to 11:00 am EST, FDA White Oak Campus, 10903 New Hampshire Avenue, Silver Spring, MD 20993; Bldg. 21, Room 1536 between Genentech, Inc. and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

XOFLUZA (baloxavir marboxil), 20 and 40 mg tablets, was approved on October 24, 2018, for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. On January 4, 2019, Genentech submitted a supplemental NDA (sNDA) to fulfill postmarketing commitment 3503-7 and to expand the patient population to include patients with acute uncomplicated influenza who are at high risk of developing influenza-related complications.

Genentech submitted a Type B, Pre-NDA/Pre-sNDA meeting request, on July 24, 2019 (NDA 210854), and July 25, 2019 (IND 126653), to discuss the results of the Phase 3 miniSTONE 2 study (CP40563) and the Phase 3 BLOCKSTONE study (1719T0834/XV41428), as well as the content and format for the planned pediatric NDA and the post-exposure prophylaxis (PEP) sNDA.

The meeting objectives include discussion of the following:

- Discussion of the topline results from the Phase 3 miniSTONE 2 study (CP40563) and the Phase 3 BLOCKSTONE study (1719T0834/XV41428)
- Agreement on the proposed stability data package to support the planned pediatric indication
- Discussion of other planning topics such as the content of the filing packages, format of the datasets, and 120 Day safety updates

2.0 DISCUSSION

The Sponsor's questions are in ***bold italicized font*** and Division's responses are in standard font.

2.1. Clinical Safety and Efficacy

Question 1 (Pediatric): Does the Agency agree that the efficacy and safety results from Study CP40563 and supporting Japanese pediatric studies provide a positive benefit-risk profile and adequate clinical evidence to support the proposed Xofluza pediatric indication?

XOFLUZA is indicated for the treatment of acute uncomplicated influenza in pediatric patients aged 1 to < 12 years old.

FDA Response to Question 1:
We cannot agree that the efficacy and safety results from Study CP40563 and the supporting Japanese pediatric studies support a pediatric indication for Xofluza until after review of the full clinical study reports and datasets from the studies. However, we

agree the results of these studies, given a positive review, are likely to support a pediatric indication.
The exact wording of the indication cannot be determined until after review of the data from these studies.

Question 2 (PEP): Does the Agency agree that the efficacy and safety results from the Phase III Study T0834 provide adequate clinical evidence and demonstrate an acceptable benefit-risk profile to support the following proposed Xofluza prophylaxis indication?

XOFLUZA is indicated for post-exposure prophylaxis of influenza in individuals aged 12 and above.

FDA Response to Question 2:
As above, we cannot agree that the efficacy and safety results from Study T0834 will support a post-exposure prophylaxis indication for Xofluza until after review of the full clinical study reports and datasets from this trial. However, we agree the results of this trial, given a positive review, are likely to support such an indication.
The exact indication cannot be determined until after review of the data from these studies.

2.2. Chemistry, Manufacturing, and Controls (CMC)

Question 3: Does the Agency agree with the proposed stability data package for baloxavir marboxil, granules for oral suspension, 2 mg/mL in particular:

a) Does the Agency agree that the NDA can be submitted with:
- ***9 months of long-term stability data at 25°C/60% relative humidity (RH) and 30°C/75% RH and six months of accelerated stability data at 40°C/75% RH from three primary stability batches?***
- ***and 12 months of long-term stability data at 30°C/75% RH and six months of accelerated stability data at 40°C/75% RH from three supportive stability batches?***

b) Does the Agency agree that the 12 month long-term stability data from the three primary stability batches can be submitted during review, by end of February 2020 at the latest?

FDA Response to Question 3:
a) We will accept the proposed stability package with 9 months long-term and 6 months accelerated stability data from the 3 primary stability batches. We will also accept the 12 months of long-term stability data for the proposed supporting batches at the time of NDA submission.

b) We will accept the 12-month long term stability data for the primary batches within 1 month of the NDA submission.

Additional comment:
It is noted that you have included the acceptance criteria for TAMC, TYMC and *E.coli* testing for the release, however, you did not include microbiology quality testing for the drug product on stability. In your NDA submission, it is recommended that you provide information to support a potential waiver of microbiology stability testing, such as bioburden control of API and excipients, microbiological control of the manufacturing process, and microbiological test results from exhibit batches produced in the intended commercial manufacturing facility. For additional information, reference is made to ICH Q6A Specifications: *Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*.

2.3. Regulatory

Question 4 (Pediatric): Does the Agency agree that Xofluza for treatment of acute uncomplicated influenza in pediatric patients aged 1 to <12 years old will likely meet the criteria for priority review?

FDA Response to Question 4:
Determination of a priority review is made at the time of filing, and we cannot comment on priority review designation at this time.

Question 5 (Pediatric): Does the Agency agree that the submission of this pediatric application supported by the pivotal CP40563 study and supporting Japanese studies meets the associated pediatric post-marketing requirements (PMRs) for NDA 210854?

FDA Response to Question 5:
Fulfillment of the PMRs will be determined after FDA review of the clinical study reports and datasets submitted with the NDA for the pediatric trials.

Question 6 (Pediatric and PEP): Does the Agency agree with providing the Development Safety Update Report (DSUR) in lieu of a 120 Day Safety Update Report to support both the Pediatric and Prophylaxis submissions?

FDA Response to Question 6:
We do not agree with the submission of a Development Safety Update Report in lieu of a 120 Day Safety Update Report. Please submit a 120 Day Safety Update Report (SUR) for both the Pediatric and Prophylaxis submissions. In your SUR, please include a tabular summary of all serious postmarketing adverse events reported since the SUR submitted in May 2019 for the supplemental NDA, S-001. Please further address any concerning adverse events, such as those events of greater severity or which were

reported at higher frequencies. In addition, please provide summaries of clinical trial and post-marketing adverse events of: hypersensitivity and related events, including anaphylaxis, angioedema, urticaria, serious cutaneous adverse events, neuropsychiatric adverse events, cholecystitis, cholelithiasis and related events, and rhabdomyolysis.
Please note that if a priority review is granted, the timeline of the SUR submission will differ.

Question 7 (Pediatric): Does the Agency agree with the Sponsor's proposal to update the USPI with information on how to administer Xofluza granules for oral suspension 2 mg/mL to allow its use in patients who have (b) (4) with difficulty swallowing tablets?

FDA Response to Question 7:

- The decision on whether to include information in the USPI regarding the administration of Xofluza granules for oral suspension 2 mg/mL in patients with (b) (4) tubes can only be made after review of the data provided to support use of Xofluza granules with (b) (4) tubes and a review of the proposed labeling.
- (b) (4)
- We recommend that you submit thorough justification for inclusion of these data in the package insert to the NDA. Please note the acceptability of administration instructions will be a review issue.
- (b) (4) If it is the latter, please note that these different situations will require separate justifications for labeling and instructions for use.

2.4. Format and Content

Question 8 (Pediatric): Does the Agency agree with the Sponsor's approach of basing the proposed pediatric indication primarily on data from the pivotal CP40563 Phase III study and incorporating data from previous Japanese pediatric studies as supportive data?

FDA Response to Question 8:
We agree with the proposed approach. We agree with not pooling data from the studies. Because different doses were used, please provide safety summaries by both dose and by exposure for all trials.

In your report and your datasets for Study T0822, please provide safety and efficacy results for the entire study population and separately for subjects weighing less than 20 kg and for those weighing 20 kg or greater.
Please provide demographic, safety, and efficacy datasets for all pediatric studies.

Question 9 (Pediatric and PEP): Does the Agency agree with the proposed content of the pediatric NDA and PEP sNDA?

FDA Response to Question 9:

- We recommend submissions for both indications (pediatric and PEP) be submitted at the same time:
  - The study reports and datasets for both the pediatric and the PEP indications should be submitted to the original NDA for the granule formulation at the same time. In addition, at the same time as the original NDA (granule formulation) submission, they should **also** be submitted as (b) (4) efficacy supplements to NDA 210854 Xofluza Tablet.
  - If the proposed indications are submitted at different times, it may be considered to be a new indication or claim to the pending original application and may incur additional user fees. Please refer to the Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.
- Your original NDA for the granule formulation should include the following:
  - CMC and bioequivalence data to support use of the 2% granules formulation
  - safety, pharmacokinetics and efficacy data from Trial CP40563 along with the supportive data from studies T0822 and T0833
  - safety, pharmacokinetics and efficacy data for study T0834 for PEP, and datasets for each study.
- The (b) (4) efficacy supplements should contain a complete module 1 and brief introductions for the regulatory need for the individual submissions. The (b) (4) efficacy supplements should not contain the clinical data but should cross-reference data in the original NDA for the granule formulation. Sufficient hyperlinks should be used to navigate between and within the submissions.

Original NDA/sNDA Content and Format

Regarding the table of contents, we have the following comments:
In Module 1 (Administrative Information):

- Please include Form 3674, Certificate of Compliance, in section 1.1 – Forms
- Form 3397 is not needed for an efficacy supplement as a user fee is not required for a Prior Approval Supplement
- Please provide a Field Copy Certification. The Field Copy Certification should be included in section 1.3.2 of the eCTD. Please notify the District office by letter that your NDA eCTD submissions have been submitted to FDA. The letter should include:

  - Drug and Application number
  - FDA Center and Division
  - Application is in eCTD format

  Please refer to the eCTD Technical Conformance Guide for guidance (accessible at https://www.fda.gov/media/93818/download)
- Patent information is required to be submitted with all new drug applications (NDAs) as provided for in 21 CFR 312, 314.53 (c)). Please submit Form FDA 3542a at the time of submission of the NDA to folder 1.3.5 - Patent and exclusivity
- Please include any letter of authorization/Drug Master File to section 1.4 – References, if applicable
- Your Agreed Amended iPSP should be placed in section "1.9.6 - Other correspondence regarding pediatric exclusivity or study plans"
- Please include your draft carton and/or container labels in section 1.14.1.1, if applicable

Module 2 (Summaries)

- Your proposal to submit the ISE and ISS based on Example 4 of the *Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009)* is acceptable. However, please provide a hyperlink to the appropriate sections where the remainder of the ISE and ISS is located:
  - The ISS should address safety by dose and by exposure. Information for the primary and supportive pediatric studies (CP40563, T0822, and T0833) as well as pediatric safety data from subjects younger than 12 years of age in the PEP trial (T0834), should be included in the ISS.
  - The ISE should include a dose justification for the U.S. population and a should provide the rationale for extrapolating efficacy between studies CP40563 T0822, and T0833.

Module 3 (Quality)

There was no description of the drug substance module. Please clarify what drug substance information will be submitted with the NDA.

Module 5 (Clinical Study Reports)

- Please include narratives for all serious adverse events, deaths, and premature discontinuations due to an adverse event, regardless of causality.
- Please provide the datasets for both the trial CP40563, as well as for the supportive pediatric studies.
- Instead of references to previous submissions, please include the protocols and Clinical Study Reports for the supportive studies in the NDA/sNDA.

Clinical Virology:

- Please provide a brief summary of genotypic data to be included in the pediatric and PEP NDA, including numbers of subjects and index patients (PEP) with baseline and post-baseline sequence data for PA, PB1, PB2, and NA genes.
- As part of the data that will be submitted to support a PEP indication, we are expecting PA sequence data for both infected household contacts and associated index patients in order to evaluate treatment-emergent resistance, potential events of transmitted resistance, and, where data are sufficient, to identify probable transmission pairs. Please include a unique household identifier for all index patients and subjects in datasets.
- For pediatric treatment studies, genotypic data should include baseline and post-baseline PA (and PB1 and PB2 where applicable), and NA sequences for subjects receiving baloxavir or a neuraminidase inhibitor, respectively. You have stated that you plan to sequence PB1 and PB2 for all subjects with a PA resistance-associated substitution, which should include all substitutions listed in the USPI. Please confirm the criteria for identifying subjects for sequencing of PB1 and PB2 in each study.
- For the pediatric and PEP NDA, resistance analysis datasets should be submitted in the same format, and generally contain the same parameters (where applicable), as those submitted for study T0832 (supplement 001). Virology datasets should be included in Module 5.

The current format for the eCTD table of contents can be found at https://www.fda.gov/media/76444/download.
Please refer to this document for the current folder headings and placement of data. In addition, if you have questions regarding the format of your eCTD submission, please contact the electronic submission staff at esub@fda.hhs.gov.

2.4. Additional Comments

Clinical

1. In the datasets submitted for each study and for each indication, please include the following in each dataset:
   - Patient treatment arm
   - Demographics (sex, age, race, and ethnicity)
   - Weight
   - Baloxavir marboxil dose
   - Study population (ITTI, PP, safety)
2. Please include either a dataset or a table describing the individual high-risk factors for subjects with high risk factors for influenza complications in the PEP trial.

Clinical Virology

3. In the final clinical study report for CP40563, please account for the 8 subjects included in the ITTI population (n=124, briefing document Table 13) and not apparently evaluated for influenza virus type/subtype (n=116, briefing document Table 14). The ITTI population should be defined by confirmation of influenza virus infection by the central-lab RT-PCR assay.

Chemistry, Manufacturing, and Controls

4. You have proposed to administer the granules after reconstitution with water. Provide in-use stability data in the submission for the proposed duration and storage conditions of the reconstituted product as described in the labeling.
5. The proposed drug product formulation is granules for oral suspension. Provide information in the submission for each excipient and the maximum amount approved in the Inactive Ingredient Database for the corresponding excipients in similar dosage forms.
6. If there were any changes to the formulation for the granules for oral suspension used in the clinical studies, provide in the NDA complete information on the batch numbers, components and composition.
7. We recommend that you provide elemental impurities data from representative batches of the drug product tested using a USP <233> method to demonstrate that the proposed controls for elemental impurities in the individual drug product components are sufficient to mitigate potential risk from elemental impurities in the drug product. If the data demonstrates that the total elemental impurity level from all sources (i.e., drug substance, excipients, processing equipment etc.) in the drug product is expected to be consistently less than 30% of the permitted daily exposure, then additional controls may not be required.

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)

You indicate Xofluza granules for oral suspension will be supplied in a glass amber bottle containing 40 mg of baloxavir marboxil, which must be constituted with 20 mL of water to yield a 2 mg/mL oral suspension. Additionally, you indicate this product is intended for single use with a suitable oral dispenser and that the proposed single dose regimen will be weight based. To better understand how you intend this product to be used please clarify the following:

1. Please clarify who the intended users are for constituting the suspension.
2. Please clarify if there are any specific considerations for handling of the product once constituted. For example, will the constituted product require refrigeration or any special storage?
3. Please clarify the timeframe in which the product must be used once constituted.

4. One bottle is proposed to deliver a single dose up to 40 mg (20 mL). (b) (4)
5. Please clarify what is meant by " (b) (4)
6. Please clarify if you intend to (b) (4) to the Agency for review.

3.0 ADDITIONAL INFORMATION

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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, 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.

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]
(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*.[4]

[4] https://www.fda.gov/media/85061/download

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/

CHRISTINE KIM
10/03/2019 10:06:24 AM