CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761108Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128367

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Mike Page
Executive Director, Regulatory Affairs
100 College Street
New Haven, CT 06510

Dear Mr. Page:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALXN1210.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2018. The purpose of the meeting was to discuss the content and format for the Biologic License Application (BLA) submission for ravulizumab in the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Acting Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	June 12, 2018 from 11:00 AM- 12:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 128367
Product Name:	ALXN1210
Indication:	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor/Applicant Name:	Alexion Pharmaceuticals, Inc.
Meeting Chair:	Tanya Wroblewski, MD
Meeting Recorder:	Natasha Kormanik, MSN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
R. Angelo de Claro, MD – Acting Deputy Director
Tanya Wroblewski, MD – Acting Clinical Team Lead
Rosanna Setse, MD, MPH, PhD – Clinical Reviewer
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V
Olanrewaju Okusanya, PharmD, MS – Clinical Pharmacology Reviewer

Office of Biostatistics/ Division of Biometrics V
Jingjing Ye, PhD – Acting Team Lead
Alexei Ionan, PhD – Biostatistics Reviewer

Office of Pharmaceutical Quality (OPQ)/ Office of Biotechnology Products
Joslyn Brunelle, PhD – Team Lead
Xuhong Li, PhD – Product Quality Reviewer

OSE/ Division of Risk Management (DRISK)
Elizabeth Everhart, MSN, RN, ACNP – Team Lead
Joyce Weaver, PharmD – Risk Management Analyst

SPONSOR ATTENDEES

Alexion Pharmaceuticals, Inc.
Lori Shafner, PhD –Vice President, Global Development Team Leader
Scott Rottinghaus, MD – Executive Medical Director, Medical Sciences
Andrew I. Damokosh, PhD – Senior Director, Biostatistics
Michael Page – Executive Director, Global Regulatory Affairs
Rajendra Pradhan, PhD – Executive Director, Head of Clinical Pharmacology
Marissa A. Bernstein, PhD – Director, Medical Writing
Arshad Mujeebuddin, MD – Senior Medical Director, Global Pharmacovigilance
Camille Métais, PharmD – Senior Director, Global Regulatory Affairs

1.0 BACKGROUND

The Sponsor states that ALXN1210 is a recombinant, humanized antibody, consisting of two identical 448 amino acid heavy chains and two identical 214 amino acid light chains.

ALXN1210 is being developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and other diseases in which complement activation is involved.

On March 19, 2018, the Sponsor requested a type B meeting to discuss the content and format for the BLA submission for ravulizumab in the treatment of PNH.

FDA sent Preliminary Comments to Alexion Pharmaceuticals, Inc. on June 4, 2018.

2. DISCUSSION

Question 1: *Does the Division agree with the proposal for presentation of efficacy data?*

Does the Division agree with the proposal that the CTD SCE can serve as the written component of the ISE in the proposed submission?

FDA Response to Question 1: Your proposal for the presentation of efficacy data is acceptable. An integrated summary of efficacy (ISE) is a required component of the application. In this situation, however, it is acceptable to include a page with a cross-reference to the summary of clinical efficacy (SCE, Module 2, section 2.7.3) in the ISE. The summary of clinical efficacy can serve as the ISE provided that the data can be included within the space limitations of the SCE.

Additional comments
Describe your plans for sensitivity analyses to evaluate the impact of treatment effect between the stratification factors selected for Study PNH-301 and our previous recommendation for evaluating different pre-study RBC transfusion requirements (1-4, >4-14, > 14 PRBC). Clarify if you intend to perform a sensitivity analysis in which transfusions are considered as a continuous covariate.

Discussion: No discussion.

Question 2: *Does the Division agree that the proposed safety analyses and presentation of safety data are appropriate to support the review of the proposed BLA?*

Does the Division agree with the proposal that the CTD SCS can serve as the written component of the ISS in the proposed submission?

FDA Response to Question 2: We agree with your plan to pool data from the phase 3 studies ALXN1210-PNH-301 and ALXN1210-PNH-302 as well as the data from studies ALXN1210-PNH-103 and ALXN1210-PNH-201 in the ISS. The Phase 3 PNH Population including patients from studies ALXN1210-PNH-301 and ALXN1210-PNH-302 will be considered the primary dataset for assessment of safety in patients with PNH.

The summary of clinical safety can serve as the ISS provided that the data can be included within the space limitations of the SCS.

Discussion: No discussion.

Question 3: *Does the Division agree with the proposed schedule and format for providing updated safety information from the ongoing studies in adult patients with PNH?*

FDA Response to Question 3: Yes, your proposal appears reasonable.

Discussion: No discussion.

Question 4: *Does the Division agree with the proposed criteria for provision of safety narratives?*

*Does the Division agree with the proposed criteria for provision of CRFs**?***

FDA Response to Question 4: Yes. Please note that narrative summaries of important AEs (e.g., deaths, events leading to discontinuation, other SAEs) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject.

Discussion: No discussion.

Question 5: *Does the Division agree with the proposal for the ravulizumab REMS?*

FDA Response to Question 5: If ravulizumab is approved, it is likely that it will require a REMS to ensure its benefits exceed its risk of meningococcal infection. We agree with submitting a draft REMS and REMS Supporting Document for ravulizumab based on the draft labeling at the time of the submission of the BLA and based on the REMS approved for eculizumab. Consider in the REMS submission whether an abbreviated ravulizumab REMS certification protocol might be appropriate for prescribers already certified in the Soliris REMS. The requirement for a REMS and the elements comprising any required REMS will be determined during the Agency review of the application.

Discussion: No discussion.

Question 6: *Does the Division agree that the proposed plan is appropriate for long-term safety data collection for the proposed BLA?*

FDA Response to Question 6: We note that the extension period for Study PNH-301 and PNH 302 are for up to 2 years. We continue to recommend that you should collect long term safety data a minimum of 5 years.

It appears from your briefing document that 5 years of follow-up safety data will only be available for the 26 patients enrolled in Study ALXN1210-PNH-201 and it is unclear if all 26 subjects are treated at the proposed dose and schedule using the to-be-marketed formulation.

Discussion: Further discussion with the Sponsor regarding long term safety data collection will occur during the review of the BLA and will likely be subject to a post marketing requirement (PMR).

(b) (4)

Question 7: *Alexion considers the Clinical Pharmacology data package for ravulizumab complete, and as such will adequately describe the Clinical Pharmacology attributes of ravulizumab. Does the Division agree?*

FDA Response to Question 7: Your clinical pharmacology package appears adequate.

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

2. What are the exposure-response relationships for efficacy, safety and biomarkers?

3. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?

4. What is the impact of immunogenicity on exposure, efficacy and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

    Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

5. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

Discussion: **No discussion.**

Question 8: *Does the Division agree with the proposal for presentation of datasets in the submission?*

FDA Response to Question 8: Please ensure compliance with the latest version of the STUDY DATA TECHNICAL CONFORMANCE GUIDE: Technical Specifications Document (March, 2018) https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Please provide the following:

- Executable, clearly commented, non-macro programs in ASCII format used to create tables and figures for primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure that programs call only data submitted to the Agency and can be easily used to reproduce the results in the CSR. Ensure that variables used in the programs for generating results in the CSR are described clearly in the define file.

- A clear index with descriptions of the programs

- Annotations for each figure and table in the CSR with a link to the program used to generate results

- Ensure that the clinical pharmacology datasets requested in response to Question 7 are provided including those relevant to the healthy volunteer studies.

Discussion: The Sponsor clarified proper documentation for connection programs as well as macros (including descriptions of variables) with table outputs will be provided in the BLA submission.

Question 9: *Does the Division agree with the proposed format for the BLA?*

FDA Response to Question 9: The proposed format for the BLA appears acceptable.

Discussion: No discussion.

Question 10: *Based on the information to be provided in the briefing document, does the Division agree that the content of the proposed submission would be adequate for review?*

FDA Response to Question 10: The topline efficacy results you provided in the meeting package for Studies PNH-301 and PNH 302 appear encouraging. The Agency will conduct our own independent analysis of the datasets submitted in the application to confirm the efficacy claims. The adequacy of your proposed submission for review will be determined at the time of filing.

Ensure that the datasets and reports requested in the response to Question 7 are included in your submission in the appropriate location. For example, it is not clear in Appendix 6 of your background material where your bioanalytical reports will be located in your submission.

Discussion: No discussion.

Additional comments

1. Your upcoming submission has been identified for an Assessment Aid. An Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the application. The Aid provides a generic structure that covers the application's key points.

   The Assessment Aid is a stand-alone document; i.e., the information and supportive evidence provided should be self-sufficient. Complementary tables and figures may be included as appropriate. The applicant's responses should be annotated with references to the detailed information in the study reports and the relevant dataset in the submission.. The applicant should submit this document as a Word document. We recommend that you not fill in excessive information in the assessment and that you follow the style of FDA reviews which are available in the public domain.

   The assessment aid template and instructions are provided in the attachment to this letter. We recommend that you submit the assessment aid document no later than 30-45 days after submission of your BLA.

2. Please provide a dataset that includes baseline transfusion data and transfusion requirements during the study for all patients enrolled in the phase 3 studies ALXN1210-

PNH-301 and ALXN1210-PNH-302 to allow for independent verification of your primary efficacy endpoint for Study 301 and secondary endpoint for Study 302.

3. As discussed during the CMC meeting held on January 23, 2018, a preliminary manufacturing schedule for both Drug Substance and Drug Product sites should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. All manufacturing sites should be ready for inspection upon submission of the BLA. If available, please provide the manufacturing schedules during the June 12 meeting.

4. To facilitate the development of clinical investigator and sponsor/monitor/CRO inspection assignments, we recommend that you submit the Bioresearch Monitoring (BIMO) Inspections dataset prior to the submission of your BLA. Please see additional details in Office of Scientific Investigations below for additional details.

5. We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Discussion: The Agency clarified the format, purpose and expected content of the assessment aide document. The Agency recommended limiting the assessment aid document to no more than 80-100 pages.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 23, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with

FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor plans to submit the BLA in its entirety.

- 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 it was concluded that a REMS is likely needed.

- 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.

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  BLA NUMBER: LATE COMPONENT - BIOMETRICS
  BLA NUMBER: LATE COMPONENT - CLINICAL
  BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  BLA NUMBER: LATE COMPONENT - NONCLINICAL
  BLA NUMBER: LATE COMPONENT - QUALITY

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.

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.

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* (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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified.

5.0 ACTION ITEMS

No action items discussed.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's responses to preliminary comments.

The Alexion comments below are provided in response to issues raised by the FDA in the Preliminary Comments received on 04 Jun 2018. Where FDA Responses and Additional Comments were provided and no response is included here, we acknowledge the input/feedback and no propose no further comment from Alexion is necessary.

Question 1: *Does the Division agree with the proposal for presentation of efficacy data?*

Does the Division agree with the proposal that the CTD SCE can serve as the written component of the ISE in the proposed submission?

FDA Response to Question 1: Your proposal for the presentation of efficacy data is acceptable. An integrated summary of efficacy (ISE) is a required component of the application. In this situation, however, it is acceptable to include a page with a cross- reference to the summary of clinical efficacy (SCE, Module 2, section 2.7.3) in the ISE. The summary of clinical efficacy can serve as the ISE provided that the data can be included within the space limitations of the SCE.

Additional comments

Describe your plans for sensitivity analyses to evaluate the impact of treatment effect between the stratification factors selected for Study PNH-301 and our previous recommendation for evaluating different pre-study RBC transfusion requirements (1-4, >4- 14, > 14 PRBC). Clarify if you intend to perform a sensitivity analysis in which transfusions are considered as a continuous covariate.

Alexion response:

The analyses based on pre-study RBC transfusion requirements were conducted and will be included in the submission. An analysis based on transfusion as a continuous covariate has not been performed.

Question 6: *Does the Division agree that the proposed plan is appropriate for long-term safety data collection for the proposed BLA?*

FDA Response to Question 6: We note that the extension period for Study PNH-301 and PNH 302 are for up to 2 years. We continue to recommend that you should collect long term safety data a minimum of 5 years.

It appears from your briefing document that 5 years of follow-up safety data will only be available for the 26 patients enrolled in Study ALXN1210-PNH-201 and it is unclear if all 26 subjects are treated at the proposed dose and schedule using the to-be-marketed formulation.

Alexion response:
We recognize the FDA request on the need for 5 year data to underwrite long term safety and propose to discuss options for provision of long term safety data at the pre-BLA meeting, bearing in mind that the provision of long-term data is likely to be the subject of a post-approval commitment.

Question 8: *Does the Division agree with the proposal for presentation of datasets in the submission?*

FDA Response to Question 8: Please ensure compliance with the latest version of the STUDY DATA TECHNICAL CONFORMANCE GUIDE: Technical Specifications Document (March, 2018)https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Please provide the following:

- Executable, clearly commented, non-macro programs in ASCII format used to create tables and figures for primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure that programs call only data submitted to the Agency and can be easily used to reproduce the results in the CSR. Ensure that variables used in the programs for generating results in the CSR are described clearly in the define file.
- A clear index with descriptions of the programs
- Annotations for each figure and table in the CSR with a link to the program used to generate results
- Ensure that the clinical pharmacology datasets requested in response to Question 7 are provided including those relevant to the healthy volunteer studies.

Alexion response:
The datasets included in the submission will be fully compliant with the Study Data Technical Conformance Guide referenced above.

Fully executable programs in ASCII format for ADaM datasets, Tables, Listings and Figures will be provided. Any macros required to execute programs to create tables and figures will also be provided. This approach was successfully employed for datasets submitted by Alexion recently as part of BLA125166/S-422, the supplemental BLA to extend the indication of Soliris (eculizumab) for the treatment of generalized myasthenia gravis.

A Table of Contents for all programs and corresponding outputs (ADaM dataset/ Table/ Figure/ Listing) will be included in the submission.

A footnote appears in every table and figure in the CSR containing the source table and figure number. In turn, the source table and figure contain the name of the program and source dataset(s) used to produce the output.

Additional comment 1

Your upcoming submission has been identified for an Assessment Aid. An Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the application. The Aid provides a generic structure that covers the application's key points.

The Assessment Aid is a stand-alone document; i.e., the information and supportive evidence provided should be self-sufficient. Complementary tables and figures may be included as appropriate. The applicant's responses should be annotated with references to the detailed information in the study reports and the relevant dataset in the submission.. The applicant should submit this document as a Word document. We recommend that you not fill in excessive information in the assessment and that you follow the style of FDA reviews which are available in the public domain.

The assessment aid template and instructions are provided in the attachment to this letter. We recommend that you submit the assessment aid document no later than 30-45 days after submission of your BLA.

Alexion response:
We anticipate providing an Assessment Aid within the timeline stipulated. As part of the pre-BLA meeting discussion, we would appreciate the opportunity to clarify the expectations of the Division with regard to the Assessment Aid to ensure that the document is optimized as fit for purpose.

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

/s/

TANYA M WROBLEWSKI
06/14/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128367

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attn: Leyla Toksoy
Director, CMC Regulatory Affairs
100 College Street
New Haven, CT 06510

Dear Ms. Toksoy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALXN1210.

We also refer to the meeting between representatives of your firm and the FDA on January 23, 2018. The purpose of the meeting was to gain Agency agreement that the proposed CMC submission content of the planned ALXN1210 BLA for ALXN1210 IV, 10 mg/mL will meet expectations for approval, (b) (4)

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 Kelly Ballard, Regulatory Business Process Manager, at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Leslie Ann Rivera Rosado, Ph.D.
Lieutenant Commander, USPHS
Product Quality Team Leader
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes, Alexion's Slide Presentation

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: CMC

Date: January 23, 2018
Time: 1:00 PM to 2:00 PM

Application Number: IND 128367

Product Name: ALXN1210
Indication: Paroxysmal Nocturnal Hemoglobinuria (b) (4)

Sponsor/Applicant Name: Alexion Pharmaceuticals, Inc.

Meeting Chair: LCDR Leslie Ann Rivera Rosado
Meeting Recorder: Kelly Ballard, M.S.

FDA ATTENDEES
LCDR Leslie Ann Rivera Rosado, Product Quality Team Leader, Division of Biotechnology Review and Research IV
Andrea Franco, Ph.D., Product Quality Reviewer, Division of Biotechnology Review and Research IV
Joslyn Brunelle, Ph.D., Product Quality Team Leader, Division of Biotechnology Review and Research IV
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Sushil Abraham, Executive Director, Technical Transfer and Biologics Process Development, Alexion
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Lori Shafner, Ph.D., Vice President, Global Development Team Leader, Alexion

Leyla Toksoy, Director, Regulatory Affairs – CMC, Alexion

1.0 BACKGROUND

To gain Agency agreement that the proposed CMC submission content of the planned ALXN1210 BLA for ALXN1210 IV, 10 mg/mL will meet expectations for approval, (b) (4)

2. DISCUSSION

Question 1:
Does the Agency agree with the plan to include both (b) (4) in the initial BLA?

Agency's Response:
The decision to include both (b) (4) in the initial BLA as commercial Drug Substance (DS) manufacturing facilities for ALXN1210 10mg/mL will be dependent on your ability to demonstrate comparability between the (b) (4) processes (b) (4) and between the clinical and commercial processes. Please be aware that if analytical comparability cannot be demonstrated, then additional non-clinical and/or clinical studies may be needed to support the introduction of (b) (4) as an additional DS manufacturing site.

In addition, based on the limited information provided in the meeting briefing package, the following comments are provided regarding the proposed process validation and comparability approach:

a) (b) (4)

b)

c) You propose to provide side-by-side comparability between DS batches listed in Table 11 of the meeting briefing package. In addition, to support analytical comparability provide the following:

a. Scientific justification for the clinical batches selected to be included in the analytical comparability assessment.
b. A list of all analytical tests and acceptance criteria for analytical comparability (with appropriate justification), which could be different from the release acceptance criteria.
c. Comparison with historical data (in control charts) (b) (4)
d. Analysis of stability trends under long-term and accelerated storage conditions.
e. For additional guidance on comparability assessments, please refer to ICH Q5E.
f. As communicated to you during the December 1, 2016 Type B meeting, the conditions used for the comparability thermal stress study should be relevant and appropriately justified.

Meeting Discussion:
The Sponsor addressed the Agency's preliminary response (b) and outlined their drug substance microbial control approach (refer to slides 6 – 9). The Agency agreed that the Sponsor's approach is acceptable.

Additionally, the Sponsor addressed the Agency's preliminary response (c) and outlined their drug substance comparability approach (refer to slides10 – 11). The Agency agreed that the Sponsor's proposed comparability approach is acceptable. However, final determination will be made upon review of the data submitted in the BLA.

Question 2a:
Does the Agency agree that the proposed strategy using Established Conditions is appropriate?

Agency's Response:
In general, your proposed format for presenting the established conditions in the BLA appears acceptable. However, at this time we cannot agree on the (b) (4)

The final determination on your proposed established conditions will be made upon review of the related information provided in the BLA.

Question 2b:
Does the Agency agree that the proposed PACMP will support (b) (4)

Agency's Response:

No, we do not agree that the proposed PACMP, as presented in the meeting briefing package, will support [redacted]

A PACMP [redacted] can be submitted with the original marketing application or as a PAS post-licensure. [redacted] Refer to the "Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biologic Products" and to "Guidance for Industry: Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products" for more information.

The following comments are provided for the proposed PACMP [redacted] as outlined in the Appendix 3 of the meeting briefing package:

a) Comparability protocols (CP) should be comprehensive and include sufficient details for the Agency to evaluate the acceptability of the CP to assess the effect of the proposed change(s) on the identity, strength, quality, purity, and potency of the product. This should include, for example, an assessment of the associated risk, specific tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the lack of adverse effect of one or more proposed CMC changes on product quality. If the product and process understanding available at the time of the original application approval is not sufficient to support the risk analysis for future changes, a CP can also be submitted as a PAS.

b) [redacted]

c)

d) (b) (4)

e)

In case you still intend to include Comparability Protocol(s) in the original BLA submission, final determination on acceptability will be made during the review of the BLA.

Question 2c:

Does the Agency agree that the approach (b) (4) ?

Agency's Response:

The approach (b) (4) might be appropriate if supported by the data and will be evaluated at the time of BLA review. (b) (4)

Question 3:

Does the Agency agree that the proposed plan (b) (4) to demonstrate LIVCA?

Agency's Response:

We do not agree with your proposal (b) (4) to demonstrate LIVCA. The limit of in vitro cell age is typically established using full-scale commercial manufacturing process conditions. (b) (4) . If you decide to pursue (b) (4) , then the information should be submitted as an IND amendment to allow the review and internal discussion on the adequacy of the proposed approach.

Meeting Discussion:

The Sponsor outlined their strategy to determine the limit of in vitro cell age (LIVCA) (refer to slides 12 – 13). The Sponsor asked whether the Agency agrees with the approach to use data generated at (b) (4) to demonstrate LIVCA.

The Agency responded that the approach for demonstrating LIVCA at (b) (4) *to support the maximum cell generation number for the commercial process at both* (b) (4) *is acceptable. However, testing for product quality attributes must be included to the list of tests outlined in slide 13 to ensure product quality at the LIVCA. The Sponsor agreed.*

(b) (4)

Question 4:

Does the Agency agree that (b) (4) would be acceptable to waive the PAI at (b) (4) specific for ALXN1210 drug product?

Agency's Response:

No, we do not agree. A decision regarding the pre-license inspection of the drug product manufacturing site will be made after BLA submission (b) (4) A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle.
All manufacturing sites should be ready for inspection upon submission of the BLA.

In addition, the BLA should include data to support the specificity of your identity test, to ensure that the test can discriminate between Soliris and ALXN1210 drug products.

Question 5:

Does the Agency agree that (b) (4)

Agency's Response:

No, we do not agree. Under PDUFA VI, you and FDA may reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. (b) (4) would not be considered such a minor component. (b) (4)

Meeting Discussion:

(b) (4)

The Agency stated that the BLA should be complete at the time of submission, (b) (4)

Question 6a:

(b) (4)

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(b) (4)

Additional Product Quality Microbiology Comments

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. This information should be provided for the manufacturing (b) (4) of the drug substance. The provided information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any (b) (4) The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification lots (3.2.S.2.5).
- (b) (4)

- (b) (4)
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for (b) (4) the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

a. The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.
   - (b) (4)

b. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:
   - (b) (4)

- [redacted] (b) (4)
- Shipping validation studies.
- Capping validation demonstrating maintenance of container closure integrity.

c. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:
   - Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
   - Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for [redacted] (b) (4) (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.
   - Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
   - Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (RSE or CSE) into undiluted drug product and then testing for recoverable endotoxin over time.
   - Microbiological studies in support of the post-dilution storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations which would be administered to patients, and use the label-recommended solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-dilution storage period is not more than [redacted] (b) (4) at 2-8°C.

Meeting Discussion:

The Agency explained to the Sponsor that the need for microbiological studies in support of a post-dilution storage period of [redacted] (b) (4) *at 2-8°C is based on prior experience with*

microbial contamination of certain biologics occurring after (b) (4). *The Agency would require data from the Sponsor in order to accept a post-dilution storage period of* (b) (4).

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/s/

LESLIE A RIVERA ROSADO
02/02/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128367

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Leyla Toksoy
Director, CMC Regulatory Affairs
100 College Street
New Haven, CT 06510

Dear Ms. Toksoy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALXN1210.

We also refer to the meeting between representatives of your firm and the FDA on December 1, 2016. The purpose of the meeting was to gain Agency alignment on the CMC development plan for ALXN1210.

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 Kelly Ballard, Regulatory Business Process Manager, at (301) 348-3054.

Sincerely,

{See appended electronic signature page}

Joslyn Brunelle, Ph.D.
Product Quality Team Leader
Division of Biotechnology Review and Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: CMC

Date: December 1, 2016
Time: 12:00 PM to 1:00 PM
Phone Arrangements: Dial-In Number: (b) (4)
Conference ID: (b) (4)

Application Number: IND 128367

Product Name: ALXN1210
Indication: Paroxysmal Nocturnal Hemoglobinuria (b) (4)

Sponsor/Applicant Name: Alexion Pharmaceuticals, Inc.

Meeting Chair: Joslyn Brunelle, Ph.D.
Meeting Recorder: Kelly Ballard, M.S.

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Joslyn Brunelle, Ph.D., Product Quality Team Leader, Division of Biotechnology Review and Research IV
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Maria Jose Lopez Barragan, Ph.D., Staff Fellow, Division of Microbiology Assessment, Branch IV
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO
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Anthony Angu, Pharmacy Student
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Megan Colley, Senior Manager, Regulatory Affairs
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William McDonald, Ph.D., Senior Director, Process Development
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Brian Molloy, Executive Director, Quality

Eric Routhier, Ph.D., Director, Pharmaceutical Development
Lori Shafner, Ph.D., Vice President, Global Development Team Leader
Leyla Toksoy, Director, Regulatory Affairs-CMC
Lorraine Whittemore, Executive Director, Regulatory Affairs-CMC

1.0 BACKGROUND

To gain Agency alignment on the CMC development plan for ALXN1210.

2. DISCUSSION

Question 1:

Development Plans

To provide additional manufacturing flexibility and to support clinical demand, this process is planned to be transferred to two additional drug substance manufacturers for clinical supply prior to completing process validation for commercial supply at the commercial drug substance manufacturing site, (b) (4) All drug product manufacturing will continue at (b) (4) An overall timeline of these development activities is provided in Figure 2.

Does the Agency agree with Alexion's plan for the introduction of additional drug substance manufacturing sites in our Phase 3 program?

Agency's Response:

The decision to introduce additional drug substance manufacturing sites into your Phase 3 program is dependent on your ability to supply ALXN1210 to patients in your pivotal studies. You should conduct a risk assessment to assess how multiple manufacturing changes could impact the outcome of your pivotal clinical studies. We recommend that you introduce material manufactured at (b) (4) as early as possible into your clinical study.

It is our understanding that your comparability exercise in your future BLA will include data from three PPQ batches manufactured at (b) (4), three batches manufactured at (b) (4) (Process A), three batches manufactured at (b) (4) (Process B), and three batches manufactured at (b) (4) (Process B). The number of batches in your comparability exercise appears adequate. Your strategy to demonstrate comparability will depend on the safety and efficacy information obtained from your pivotal clinical studies.

You have not provided sufficient information to support that the thermal stress study (b) (4) is the only relevant condition to include in your comparability exercise. You should explore other stressed conditions in order to fully characterize the degradation pathways for your product and provide data to justify the stressed condition(s) chosen for the comparability exercise.

Meeting Discussion:

Refer to slides 5-9, where the sponsor outlined their comparability strategy for the IND amendments and for the future BLA submission. The sponsor asked if the proposed approach is acceptable.

The Agency responded that the adequacy of the approach cannot be determined until the comparability data is reviewed. For the future BLA submission, a minimum of 3 batches should be included in the comparability exercise. The sponsor should provide a justification for how the batches were chosen for the comparability exercise. In addition, the sponsor should submit all historical data from batches produced at the three manufacturing sites (b) (4) ***and specify which batches were used in the clinical study. Final determination will be made upon review of the data and the justification provided in the BLA.***

Question 2:

Drug Substance and Drug Product Specifications

Commercial specifications will be based on an analysis of drug substance and drug product data from clinical batches manufactured using both Process A and Process B.
Does the Agency agree that the proposed path for defining drug substance and drug product specifications for release and stability is appropriate to support the submission of a BLA?

Agency's Response:

The general approach for establishing specifications for the commercial product should include data from all batches used in the clinical studies, provided that comparability can be established among the drug substance lots manufactured at 3 different sites (b) (4)
However, your current Drug Substance and Drug Product specifications are not acceptable for a product proposing major manufacturing changes during the pivotal clinical study.

a. The current acceptance criterion for imaged capillary electrophoresis is (b) (4) These criteria do not adequately control for charge variants. Based on chromatograms provided in Figure 11 and Figures 32-36 (page 104 and 119-123 of your meeting package), you can establish quantitative acceptance criteria for the percent area of main, acidic, and basic species. Therefore, revise the acceptance criterion for imaged capillary electrophoresis accordingly.

b. The current acceptance criterion for the oligosaccharide profiling is (b) (4) . These criteria do not adequately control for possible variability in the oligosaccharide profile. Based on the chromatogram provided in Figure 13 (page 106 of the background package), (b) (4) In addition, provide justification for monitoring only the FA2, FA2G1, and FA2G1' species when there are six glycan species identified in the chromatogram (including FA1, A2, FA2, Man5, FA2G1, FA2G1').

c. The acceptance criteria for the C5 binding assay and hemolytic assay are currently (b) (4) respectively. These acceptance criteria are unusually broad for the current stage of development and may not provide sufficient control over product potency to ensure consistent dosing. Therefore, tighten the acceptance criteria to more adequately reflect your clinical and manufacturing experience.

d. The Agency notes that the hemolytic assay is performed only during release testing, and it is not included in the stability testing. Include the hemolytic assay during stability testing or provide a justification for excluding the assay.

e. The hemolytic assay measuring rabbit red blood cell lysis appears to be modified compared to the version used for Eculizumab. Clarify whether you explored alternative assays formats based on the technologies currently available. Provide justification to support the adequacy of the current hemolytic assay to monitor potency for ALXN1210.

f. The current acceptance criterion for peptide mapping is (b) (4) Specifications should be objective and quantitative whenever possible because objective criteria allow for consistent evaluation of product quality. Therefore, revise the criteria for peptide mapping (b) (4) .

g. The current acceptance criteria for reduced and non-reduced CE-SDS are (b) (4) However, the criteria do not include a quantitative limit for impurities. Therefore, revise the acceptance criteria for the reduced and non-reduced CE-SDS by include a quantitative limit for impurities.

h. The drug substance specification for bioburden (b) (4) is considered adequate based on the recommended DS storage conditions. The sterility specification for drug product lot release is adequate. The DS and DP release specifications for endotoxin (b) (4) are aligned and appear adequate; however, the final acceptability will be addressed as a review issue.

Meeting Discussion

Refer to slide 11, where the sponsor acknowledged the FDA comments and proposed to submit revised specifications for the imaged capillary electrophoresis, oligosaccharide profiling, CE-SDS, and C5 binding assays in the next IND amendment. The Agency responded that the adequacy of the revised specifications will be determined after reviewing the information in the IND amendment.
Refer to slides 12-13, where the sponsor provides information regarding the hemolytic assay and states that the specification cannot be revised at this time. The Agency responded that detailed information on the hemolytic assay, including any qualification and/or validation studies that have been conducted to date, should be submitted in an IND amendment.

The Agency will provide additional feedback on the specifications, if necessary, after the review of the information submitted in future IND amendment(s).

Question 3:

Drug Substance Process Validation

Drug substance validation is planned to be initiated in Q2 2017 at the (b) (4) commercial scale at (b) (4)

Does the Agency agree that the planned process validation package for drug substance is appropriate to support an approvable BLA?

Agency's Response:

Your general plan for Drug Substance process validation appears reasonable. However, final concurrence that the validation package is sufficient to support licensure will depend on the complete package of information submitted in the future BLA.

From a microbial control perspective, the process validation strategy appears to be acceptable. For further guidance on process validation from a microbial quality perspective, refer to the additional comments section.

Question 4:

Drug Product Process Validation

Drug product validation is planned to be initiated in Q3 2017 at (b) (4).

Does the Agency agree that the planned process validation package for drug product is appropriate to support an approvable BLA?

Agency's Response:

Your general plan for Drug Product process validation appears reasonable. However, final concurrence that the validation package is sufficient to support licensure will depend on the complete package of information submitted in the future BLA.

From a microbial control perspective, the overall strategy for ALXN1210 DP process validation appears to be acceptable. Refer to the additional comments section for further guidance on process validation from a microbial quality perspective.

Question 5:

Drug Substance Stability and Proposed Expiry

The BLA will include stability data available from representative drug substance batches used in clinical studies as well as the PPQ batches.

Does the Agency agree that the proposed stability strategy will support the proposed (b) (4) expiry for drug substance?

Agency's Response:

The available drug substance stability data may not support the proposed (b) (4) expiry for drug substance.

The expiry for Drug Substance should be established using real time stability data from lots produced using the commercial manufacturing process and stored in the container closure intended for the commercial product. Based on the information you have provided, there will only be 9-12 months of stability data from DS lots manufactured at (b) (4) at the time of the BLA submission. Due to the change in the scale and manufacturing site, it is unclear whether Process B DS lots produced at (b) (4) or (b) (4) could be considered representative of the commercial manufacturing process at (b) (4)

During the review of the BLA, the Agency may request a "simple stability update" which is defined as stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA/NDA. Simple stability updates submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf life determinations.

Meeting Discussion
Refer to Slide 14, where the sponsor outlines their approach for establishing drug substance shelf-life. The Agency stated that the final determination regarding shelf-life will be made upon review of the stability data and the comparability exercise submitted in the BLA.

Question 6:
Drug Product Stability and Proposed Expiry
The BLA will include stability data available from representative drug product batches used in clinical studies as well as the PPQ batches.
Does the Agency agree that the proposed stability strategy will support the proposed (b) (4) expiry for drug product?

Agency's Response:
The available drug product stability data is unlikely to support the proposed (b) (4) expiry. The expiry for Drug Product should be established using real time stability data from lots produced using the commercial manufacturing process (b) (4) and stored in the container closure intended for the commercial product (30mL vial). Based on the information you have provided, there will only be 12-18 months of stability data from DP lots manufactured at (b) (4) at the time of the BLA submission.

You have not provided enough information on the manufacturing processes at (b) (4) for the Agency to determine whether any of the stability data from lots manufactured at (b) (4) could be considered representative of the commercial manufacturing process. Furthermore, the container closure and fill volume at (b) (4) (b) (4) vial) is not representative of the intended commercial drug product (300mg/30mL in 30mL vial).

During the review of the BLA, the Agency may request a "simple stability update" (as described in Response to Question 5).

Regarding your overall stability plan from a microbiology quality perspective, we note that endotoxin and sterility tests need not be conducted on stability samples as long as a validated container closure integrity test is conducted annually and at expiry.

Meeting Discussion:
Refer to slide 15, where the sponsor outlines their approach for establishing drug product shelf-life. The Agency stated that the final determination regarding shelf-life will be made upon review of the stability data and the comparability exercise submitted in the BLA. The Agency stressed that batches used to support expiry should be fully representative of the commercial manufacturing process.

Additional comments:

1. We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

   I. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the BLA (3.2.A) as background information for the pre-license inspections.

   Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

   II. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited to the following:

   a. (b) (4)

   b.

   c.

d. (b) (4)

e.

f.

g.

h.

III. The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information related to microbial control (b) (4) should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

a. (b) (4)

b.

c.

d.

e.

f.

g.

h.

i.

Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

a. Bacterial filter retention study for the sterilizing filter.
b. Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three most recent requalification studies and describe the requalification program. For information located in Drug Master Files (DMFs), provide Letters of

Authorization which list the relevant depyrogenation and sterilization sites and which clearly identify the location of the relevant information within the DMF.

c. (b) (4)

d.

e.

f.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

g. Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.
h. Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21CFR610.13(b).
i. Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time.
j. Container closure integrity (CCI) testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. CCI method validation should demonstrate that the assay is sensitive enough to detect small breaches (generally ≤ 20 microns) which could allow microbial ingress. CCI testing should be performed *in lieu* of sterility testing for stability samples every 12 months until expiry.

Meeting Discussion

Refer to slide 16, where the sponsor seeks clarification on additional product quality microbiology comment IIc. The sponsor asked if the proposed approach to validate process (b) (4) ***is acceptable. The Agency agreed.***

Alexion introduced an additional topic for discussion.

The sponsor asked if (b) (4) ***can be used to establish the limit of in vitro cell age. The Agency could not agree to this approach because it would represent a change in Agency policy. The limit of in vitro cell age is typically established using the full –scale commercial manufacturing process. If the sponsor decides to pursue*** (b) (4) ***, then the Agency suggests submitting information*** (b) (4) ***as an IND amendment. The Agency could review the information and internally discuss whether Alexion's approach would be acceptable.***

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/s/

JOSLYN K BRUNELLE
01/03/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128367

MEETING MINUTES

Alexion Pharmaceuticals, Inc.
Attention: Megan Colley, MPH
Senior Manager, Regulatory Affairs
55 Cambridge Parkway
Suite 800
Cambridge, MA 02142

Dear Ms. Colley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALXN1210.

We also refer to the meeting between representatives of your firm and the FDA on July 18, 2016. The purpose of the meeting was to discuss the Phase 3 dose, the details of the planned Phase 3 trials for patients with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) , and the overall development plan for ALXN1210.

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 Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4367973

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:	July 18, 2016 from 2:00-3:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 128367
Product Name:	ALXN1210
Indication:	For the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4)
Sponsor/Applicant Name:	Alexion Pharmcauticals, Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Rachel McMullen, MHP, MHA

FDA ATTENDEES

Office of Hematology Oncology Products (OHOP)/ Division of Hematology Products
Edvardas Kaminskas, MD – Deputy Director
Albert Deisseroth, MD, PhD – Clinical Team Lead
Donna Przepiorka, MD, PhD – Acting Clinical Team Lead
Pat Dinndorf, MD – Clinical Reviewer
Thomas Iype, Pharm D - Regulatory Health Project Manager
Rachel McMullen, MPH, MHA – Regulatory Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD – Team Lead
Matthew Thompson, PhD – Reviewer

Office of Biotechnology Products
Joslyn Brunelle, PhD – Team Lead
Andrea Franco, PhD – Reviewer

Office of Clinical Pharmacology
Bahru Habtemariam, PharmD – Team Lead

Office of Biostatistics/ Division of Biometrics V
Lei Nie, PhD – Team Lead
Yun Wang, PhD – Reviewer

SPONSOR ATTENDEES

Steven Ryder, MD – Senior Vice President and Chief Development Officer
Lori Shafner, PhD – VP, Global Development Team Leader
Chris Mix, MD – Executive Director, Global Medical Sciences
Scott Rottinghaus, MD – Executive Director, Global Medical Sciences
Rajendra Pradhan, PhD – Senior Director, Clinical PK/PD
Megan Colley, MPH – Senior Manager, Regulatory Affairs
Jill P. Hillier, PhD – Vice President, Regulatory Affairs
Michael Page – Senior Director, Regulatory Affairs
Martine Zimmerman, PharmD – Senior Vice President, Head of Global Regulatory Affairs
Arshad Mujeebuddin, MD – Senior Medical Director, Pharmacovigilance
Andrew Damokosh, PhD – Senior Director, Biostatistics

1.0 BACKGROUND

The Sponsor states that ALXN1210 is a recombinant, humanized antibody, consisting of two identical 448 amino acid heavy chains and two identical 214 amino acid light chains.

ALXN1210 is being developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and other diseases in which complement activation is involved.

On May 5, 2016, the Sponsor requested an End-of-Phase 2 meeting to discuss the Phase 3 dose, the details of the planned Phase 3 trials for patients with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) and the overall development plan for ALXN1210.

FDA sent Preliminary Comments to Alexion Pharmaceuticals Inc. on July 13, 2016.

2. DISCUSSION

2.1. Chemistry, Manufacturing and Controls

Question 1: Does the Agency agree with the proposed comparability strategy and plan for transitioning from Process A to Process B during the Phase 3 program?

FDA Response to Question 1: Your proposed comparability strategy and plan for the transition from Process A to Process B during the Phase 3 program appears acceptable. However, the final determination will be made upon review of the information in the future IND amendment. The cover letter for your amendment should specify the proposed date the Process B material is intended to be used in the Phase 3 program.

The meeting package indicates that a new Cell Bank will be established to ensure clonality. Please note that your future IND amendment should include specific information on the cloning process. Indicate which technique was used, such as limited dilution, flow cytometry, cell sorter, or cell imager. If limited dilution was performed, specify the number of rounds and the plating density. If cell sorting and/or imaging technologies were used, include a detailed description of how the cells were sorted, process parameters, images, training of analysts, etc. Finally, describe how clones were expanded, assessed, and selected as the final master cell bank.

Discussion: *There was no discussion.*

2.2. Non-Clinical

Question 2: Does the Agency agree that the existing nonclinical package is sufficient to support the registration of ALXN1210 and that additional nonclinical studies will not be required for approval of product in the US?

FDA Response to Question 2: The nonclinical package appears to be sufficient to support the registration of ALXN1210. The adequacy of the nonclinical studies will be a review issue.

Discussion: *There was no discussion.*

2.3. Clinical

Preamble: For Protocol ALXN1210-PNH-301, you plan to conduct a randomized noninferiority comparison of ALXN1210 to eculizumab for treatment of patients with PNH not previously exposed to a complement inhibitor. In our opinion, the protocol as designed would not support a marketing application for the indication "treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) (b) (4) We have the following comments on the design elements for the proposed study:

a) The eligibility criteria as written will not allow you to fulfill the constancy assumption. For TRIUMPH, patients were required to have at least 4 transfusions in the prior year, but there is no prior transfusion requirement in the eligibility criteria for ALXN1210-PNH-301.

Discussion: *The Sponsor agreed that the change in the patient population would violate the constancy assumption. They propose to use registry data to determine the rate of transfusion avoidance for the subgroup of patients treated prior to requiring transfusions and to cap accrual of this subgroup to 30%. FDA could not comment on the proposal, since no registry data had been submitted for review.*

b) The determination of clinical benefit for eculizumab was based primarily on the endpoint of hemoglobin stabilization in TRIUMPH. You propose to use transfusion avoidance as one co-primary endpoint in ALXN1210-PNH-301, but such an endpoint, without an objective component such as hemoglobin level, is subject to bias, since it allows investigators to choose to transfuse or withhold a transfusion without regard to the hemoglobin level. The results would be especially suspect in an open-label trial.

Discussion: *The Sponsor proposed to add transfusion guidelines in the protocol. FDA indicated that would not be sufficient to prevent bias. The Sponsor agreed to add a prespecified hemoglobin level to the definition of transfusion avoidance, making the endpoint more similar to hemoglobin stabilization.*

c) In TRIUMPH, hemoglobin stabilization was achieved by 49% (95% CI 33% - 65%) of the study subjects, and transfusion avoidance was achieved by 51% (95% CI 36% - 67%). In ALXN1210-PNH-301, you propose to use (b) (4) percentage points as the NI margin for the endpoint transfusion avoidance. Given the serious nature of PNH and the established salutary effects of eculizumab in the treatment of this disorder, your proposed margin of (b) (4) percentage points is considered greater than the largest clinically acceptable difference for the endpoints of either hemoglobin stabilization or transfusion avoidance.

Discussion: *FDA questioned why the NI margin was based on the point estimate rather than the variability of the historical outcome. The Sponsor explained that feasibility limited the sample size. They further indicated that they expected that ALXN1210 might be superior to eculizumab. The potential use of an adaptive design was raised, and FDA agreed that a protocol with an adaptive design, if designed adequately, could be used as the basis for a marketing application.*

d) You propose to use percent change in LDH as the second co-primary endpoint in ALXN1210-PNH-301. There is no basis for assuming that the percentage change in LDH reflects clinical benefit. A clinically meaningful reduction in hemolysis would be reflected by a normal or near normal LDH instead.

Discussion: *The Sponsor reasserted that percentage reduction in LDH was a benefit, since it correlated with symptoms. FDA requested that the Sponsor use the eculizumab data to identify an LDH level that corresponded with hemoglobin stabilization and to show the correlation between symptoms and percentage LDH reduction as well as with absolute LDH level. FDA requested that the results of these analyses be submitted to this IND for review.*

For Protocol ALXN1210-PNH-301 to be considered further, you would need to revise the study to address the points above.

We acknowledge that since the approval of eculizumab for treatment of PNH, the standard of care may have changed somewhat with regard to the transfusion requirements prior to start of treatment with eculizumab in the community, so it may be challenging to accrue to a protocol with a prior transfusion requirement similar to that of TRIUMPH. We further acknowledge that a smaller NI margin might increase the sample size for a noninferiority study to a level that would make a study in the untreated population unfeasible. We therefore suggest that you might also consider a randomized trial in patients already responding to eculizumab to determine if ALXN1210 would be noninferior to continuing eculizumab for hemoglobin stabilization. Given that a washout period would be needed after randomization, we recommend that the treatment duration for such a study would be at least 1 year. Alternatively, if you have preliminary data that suggests ALXN1210 is better than eculizumab in the proportion of patients with hemoglobin stabilization, you might also consider a superiority trial. If you will continue to use non-

inferiority design for your revised study, you need to provide justification for the non-inferiority margins, for primary and key second efficacy endpoints, that they will be no greater than the largest clinically acceptable differences in those corresponding endpoints.

Discussion: *The Sponsor explained that a study of patients with treatment-naive PNH was chosen, because it was felt that the results of response induction would be more meaningful to healthcare providers than maintenance of a response. FDA clarified that since the disease process was on-going, a demonstration of noninferiority in hemoglobin stabilization and LDH level in the appropriate population might be considered more than just maintenance, especially if there are additional safety and activity data for the proposed dose and schedule in a cohort from an early phase trial in treatment-naive patients with PNH.*

Question 3 regarding PNH: Does the Agency agree that the proposed inclusion and exclusion criteria for the study are adequate to support registration of ALXN1210 for the treatment of patients with PNH?

FDA Response to Question 3: See the Preamble above regarding the PNH pivotal trial.

Discussion: *See Discussion for the Preamble.*

(b) (4)

Question 4: For the PNH (b) (4) pivotal trials, does the Agency agree with the sample size and, in particular, with the selection of the non-inferiority margin?

FDA Response to Question 4: See the Preamble above regarding the PNH pivotal trial.

(b) (4)

Discussion: *See Discussion for the Preamble.*

Question 5: Is the proposed open-label design of the PNH pivotal study, because of the clear differences in dosage regimen between ALXN1210 and eculizumab, acceptable to the Agency?

FDA Response to Question 5: The open-label design for the PNH clinical trial is acceptable for the reasons you have outlined. However, the open-label design will make interpretation of the quality-of-life endpoint problematical.

Discussion: *There was no discussion.*

(b) (4)

Question 7: Does the Agency agree that, provided results demonstrate non-inferiority to eculizumab, this randomized, controlled study will be sufficient to support the approval of ALXN1210 for treatment of PNH?

FDA Response to Question 7*:* See the Preamble above regarding design of the PNH pivotal trial. A single, adequate and well-controlled, randomized, noninferiority trial might support approval of ALXN1210, but this will be a review issue.

Discussion: *There was no discussion.*

(b) (4)

Question 9: Does the Agency agree with the dosage regimen for the Phase 3 study in patients with PNH (b) (4)

FDA Response to Question 9: No. Your proposed dose is too high.

Your proposed dose of 3000 mg loading dose/3600 mg maintenance dose does not appear to predict any additional benefit for patients weighing < 100kg when compared to the 2100 mg/2700 mg dose. While it is not clear what proportion of adult patients with PNH will fall in the > 100 kg, given the mean (%CV) of 73.7 ± 14.8 kg, and the distribution of weights in patients in your previous trials, the proportion of patients weighing > 100 kg is small. You should select a dose that is predicted to be efficacious in a majority of your patients without exposing those with lower weights to really high doses without any additional benefit. In order to make an adequate assessment of the dose, we recommend that the following:

1. You use a distribution of weights more reflective of your patient population in your simulation. Given the small overall sample size of the population, a parametric distribution of weights may not be appropriate. It is not clear if this was used in your simulation.
2. You should use a 90% CI or PI, evaluating 5% alpha at the lower tail, given that low troughs are the primary concern and not high trough values
3. You should consider weight based dosing for all patients or for patients > 100 kg.

In addition to your simulation exercise, your dose selection decision should be supported by the safety and efficacy results of your ongoing studies (studies 103 and 201). Your selected dose should be the lowest dose that provides maximal clinical effect and should show preliminary evidence of balanced benefit risk profile. We are concerned that complete suppression of complement activity could compromise the innate immune response.

Discussion: *The Sponsor stated that their objective was to use a dose of ALXN1210 that resulted in rapid, complete and sustained inhibition of C5 activity. They explained their rationale for dose selection over the range of weights in the adult population, and they reviewed the results of simulation studies that used data from the early phase protocols with less frequent dosing. FDA expressed concern over the potential for overdosing patients in the lowest weight range (40-70 kg), which might fit better with the higher weight range in the pediatric population, albeit necessitating multiple weight categories for dosing. The Sponsor agreed that exposure was affected by weight, but explained further that, based on the eculizumab data, the exposure-safety relationship for ALXN1210 was expected to be flat, and that the risks of adverse events at higher exposure were mitigated by the REMS program and outweighed by the benefits of sustained inhibition of C5 activity. FDA acknowledged the simulation results but indicated that final advice regarding the dose for the pivotal trials would require review of the actual data from the study of dosing every 8 weeks. The Sponsor agreed to provide that data.*

Question 10: Does the Agency agree that this safety database is adequate to support the filing of ALXN1210 for registration in patients with PNH (b) (4)

FDA Response to Question 10: It is not possible to confirm the size of the safety database needed to address all labeling issues at this time. In general, since your treatment is recommended to be given life-long, you will need to provide data from patients on therapy using the proposed dose-schedule for at least 1 year to generate intermediate-term safety information, and we recommend that you plan ultimately for at least 5 years of follow-up for safety in the patients on the pivotal trials. Requirements for study of additional subjects at the dose-schedule to be used in labeling will depend on findings in the review of safety when the BLA is submitted. We suggest that you revisit this issue at a pre-BLA meeting when you have safety data for the proposed dose-schedule from the pivotal trials.

Discussion: *There was no discussion.*

Question 11: Does the Agency agree that the proposed clinical pharmacology development program is sufficient to support the registration of ALXN1210?

FDA Response to Question 11: No. Your proposed phase 3 doses are not acceptable. See response to question 9.

Discussion: *There was no discussion.*

3.0 OTHER IMPORTANT INFORMATION

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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/Guidance

s/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@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 (cder-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 http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

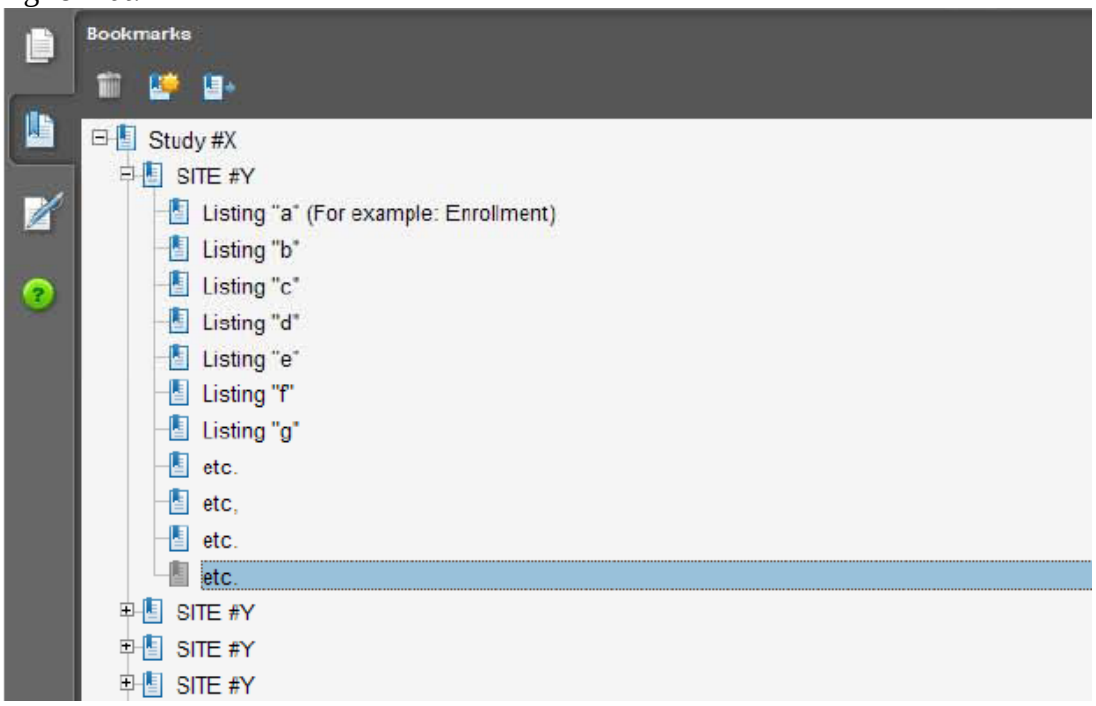
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's presented slides is attached.

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/s/

DONNA PRZEPIORKA
07/20/2016