

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217171Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 124784

MEETING MINUTES

Apellis Pharmaceuticals, Inc.
Attention: Ms. Valerie Goguen
Director, Regulatory Affairs
100 5th Avenue, 3rd Floor
Waltham, Massachusetts 02451

Dear Ms. Goguen:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for APL-2 (pegcetacoplan ophthalmic solution). We also refer to the telecon between representatives of your firm and the FDA on January 21, 2022. The purpose of the meeting was to discuss the content and format of the planned NDA submission for APL-2 for the treatment of geographic atrophy secondary to age-related macular degeneration.

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

If you have any questions, please call Wendy Streight, PhD, Regulatory Health Project Manager at 240-402-6498.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 21, 2022; 12:30 PM – 1:30 PM (EST)
Meeting Location: Teleconference

Application Number: IND 124784
Product Name: APL-2 (pegcetacoplan ophthalmic solution)
Indication: treatment of geographic atrophy secondary to age-related macular degeneration (AMD)

Sponsor Name: Apellis Pharmaceuticals, Inc. (Apellis)
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Wendy Streight, PhD

FDA ATTENDEES

Charles Ganley, MD	Director, OND/Office of Specialty Medicine (OSM)
Alex Gorovets, MD	Deputy Director, OND/OSM
Wiley Chambers, MD	Director, Division of Ophthalmology (DO)/OSM
William Boyd, MD	Deputy Director, (DO/OSM)
Jennifer Harris, MD	Clinical Team Leader, DO/OSM
Rhea Lloyd, MD	Clinical Team Leader, DO/OSM
Martin Nevitt, MD	Clinical Reviewer, DO/OSM
David Summer, MD	Clinical Reviewer, DO/OSM
Greg Soon, PhD	Statistics Team Leader, Office of Biostatistics/Division of Biometrics IV
Chunchun Zhang, PhD	Acting Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/Division of New Drug Products/New Drug Products Branch III
Daniel Schu, PhD	Product Quality Microbiology Reviewer, OPQ/ Division of Microbiology Assessment Branch 2
Lori Kotch, PhD	Supervisor, Pharmacology/Toxicology, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM)
Erin Ruhland, PhD	Pharmacology/Toxicology Reviewer, DPT-RPURM/SM
Suneet Shukla, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)

Ping Ji, PhD	Clinical Pharmacology Team Leader, OCP/DIIP
Da Zhang, PhD	Clinical Pharmacology Reviewer, OCP/DIIP
Wendy Streight, PhD	Regulatory Health Project Manager, Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Specialty Medicine (DROSM)
Milalynn Victorino, FNP-C	Regulatory Project Manager, ORO/DROSM
Valerie Vaughan, PharmD	Team Lead Pharmacist, Office of Medication Error, Prevention and Risk Management, Division of Medication Error, Prevention and Analysis
Oyinlola Fashina, PharmD	Senior Regulatory Project Manager, Office of Surveillance and Epidemiology/Project Management Staff

APELLIS ATTENDEES

Temitayo Ajayi, MD	Vice President, Clinical Development
Caleb Bliss, MA, PhD	Director, Biostatistics
Eric de Groh, PhD	Senior Manager, Medical Writing
Jeffrey Eisele, MA, PhD	Chief Development Officer
Mara Furlow, MS, RAC	Vice President, Regulatory Affairs
Valerie Goguen	Director, Regulatory Affairs
Federico Grossi, MD, PhD	Chief Medical Officer
Kate Lane, PhD, DABT	Vice President, Nonclinical Development
Shisheng Li, PhD	Director, Clinical Pharmacology
Patricia Meuse	Senior Director, Indication Lead
Patrick Murphy, MSc	Senior Director, Regulatory Affairs
Ramiro Ribeiro, MD, PhD	Senior Medical Director, Clinical Development, Ophthalmology
Jason Raines, MD	Vice President, Biometrics and Data Management
Chunlei Ke, PhD	Senior Director, Biostatistics
Kuldev Singh, MD, MPH	Consultant, Professor of Ophthalmology
Tuan Dong Si, MD	Senior Vice President, Global Drug Safety and Pharmacovigilance

BACKGROUND

APL-2 (a PEGylated peptide) is a small 13-amino-acid cyclic peptide with 12 natural amino acids and a single synthetic amino acid (methyltryptophan), covalently coupled via a linker to each end of a linear 40kDa polyethylene glycol (PEG40) chain; there are two peptide moieties per molecule of APL-2. The tridecapeptide moiety in the drug molecule binds to complement C₃ and is a broad inhibitor of the complement cascade. APL-2 is currently being developed for the treatment of geographic atrophy secondary to age-related macular degeneration.

Apellis Pharmaceuticals, Inc. (Apellis) submitted a November 3, 2021, Pre-NDA meeting request to discuss the content and format of the planned NDA submission for APL-2. A Meeting Request Granted letter was sent to Apellis on November 8, 2021. The meeting

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

package was received on December 17, 2021. The Agency sent Apellis the Meeting Preliminary Comments on January 12, 2022, and in preparation for the January 21, 2021, teleconference, Apellis requested to focus the discussion on question 1 regarding the proposed content of the 120-day safety update. The slides presented during the teleconference are included in the Attachments and Handouts section below.

DISCUSSION

Following, in **bold**, are the questions submitted in the December 17, 2021, meeting package. The FDA responses to these questions are in *italics* and the meeting discussion is in normal font.

CLINICAL

- 1. Does the Division agree that the proposed content of the 120-day safety update is appropriate to support review of the NDA for IVT pegcetacoplan for GA?**

FDA Response: *We recommend that the initial NDA submission use the day that the last patient completes his/her 18 month evaluation. The 120-day safety update should include all additional safety information that would significantly inform any changes to the labeling since the time of the 18 month evaluation.*

Meeting Discussion: *Apellis requested clarification of the Agency's request for 18 month safety data to be included in the NDA submission. The Agency stated that there is a greater likelihood of having an approvable application based on 18-month data than 12-month data and recommended that Apellis consider this when preparing to submit the application. Apellis proposed options for the submission of the safety data (see slide 3 presented in the Attachment and Handout Section).*

The Agency asked Apellis for clarification of the statement regarding the full safety data as opposed to the full data set through 18 months since there is no distinction in ophthalmology between parameters such as visual acuity that address both safety and efficacy. Apellis clarified that the primary endpoint was pre-specified at Month 12 and stated that the initial proposal is to include efficacy data up to Month 18 and Month 12 safety data assessments such as BCVA but did not plan to include secondary endpoints such as microperimetry or reading speed in the post-Month 12 analyses. The Agency stated that microperimetry is important for both safety and efficacy.

The Agency explained that it was important for applicants to include all relevant safety information in the application to ensure that new issues can be addressed during the review cycle. Therefore, it is important that Apellis submit as much as possible in the initial NDA submission. The purpose of the 120 day safety update is to ensure that any events that would be important to the labeling be shared with the Agency during the review cycle.

Apellis clarified that the company plans to prepare a 12-month and a 24-month CSR for both studies and asked if it was the intention of the FDA that an 18-month CSR be included with the initial NDA submission, or whether the 18-month data could be provided in a more summarized format. The Agency recommended that Apellis submit full datasets through Month 18, and brief summaries of key findings (not a full CSR) at Month 18. The Agency explained that reading speed is not needed at Month 18; however, microperimetry is important and should be included. Apellis agreed to provide data through Month 18 for lesion growth, safety, and microperimetry, and some data beyond Month 18 which Apellis would consider to be informative. The Agency agreed with Apellis's proposal. Apellis stated that they plan to submit the NDA before July 2022.

CLINICAL PHARMACOLOGY

2. Does the Division agree that the proposed clinical pharmacology package is adequate to support review of the NDA for IVT pegcetacoplan for GA?

FDA Response: *We acknowledge that you have assessed the IVT pegcetacoplan PK and/or PD of in five clinical studies in subjects with AMD utilizing various formulations. In each of these five studies you've assessed systemic concentrations of pegcetacoplan and/or immunogenicity. In addition, a PopPK model will be developed for characterizing IVT pegcetacoplan PK and the exposure-response (E-R) of IVT pegcetacoplan is planned to be explored. We also acknowledge you've conducted in vitro studies to investigate the clinical drug-drug interaction potential. These conducted and planned clinical pharmacology studies appear reasonable to support the filing of your NDA; however, the relevance and adequacy of your study data to support your NDA application will be determined at the time of NDA review.*

In your NDA you should submit the bioanalytical method validation and bioanalysis reports as well as information to support long-term storage stability of your PK samples and incurred sample re-analysis for review.

Meeting Discussion: No discussion was requested.

NONCLINICAL

3. Does the Division agree that the proposed nonclinical package is adequate to support review of the NDA for IVT pegcetacoplan for GA?

FDA Response: *We agree.*

Meeting Discussion: No discussion was requested.

GENERAL NDA CONTENT AND FORMAT

4. Does the Division agree that the proposed content and format of the NDA for IVT pegcetacoplan for GA, including the overall eCTD table of contents and proposed presentation of electronic data, is acceptable?

FDA Response: See response to Question 1. The proposed content and format is otherwise acceptable.

Meeting Discussion: No discussion was requested.

PEDIATRIC

- 5. Does the Division agree that Apellis has a reasonable basis to apply for a full waiver of Pediatric Research Equity Act requirements for IVT pegcetacoplan for GA because the necessary pediatric studies are impossible or highly impactable?**

FDA Response: Yes.

Meeting Discussion: No discussion was requested.

ATTACHMENTS AND HANDOUTS

The slides presented at the January 21, 2022, teleconference are included below.

(b) (4)

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

/s/

WILEY A CHAMBERS
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: December 5, 2017, 12:00 pm – 1:00 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 124784
Product Name: APL-2 intravitreal injection
Indication: geographic atrophy secondary to AMD
Sponsor/Applicant Name: Apellis Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 5, 2017 between Apellis Pharmaceuticals, Inc, and the Division of Transplant and Ophthalmology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Following, in **bold**, are the questions submitted in the October 23, 2017, meeting package. The FDA responses to these questions are in *italics*.

CLINICAL

Apellis is proposing to conduct two identical Phase 3, prospective, multicenter, randomized, double-masked, sham-injection controlled studies to assess the efficacy and safety of multiple IVT injections of APL-2 in patients with GA secondary to AMD. The protocols are designed to be adequate and well-controlled in accordance with 21 CFR 314.126 and are intended to provide the primary evidence of efficacy and safety to support the indication of ‘treatment of patients with GA secondary to AMD.’

- 1. Does the Agency agree with the proposed study design, population and inclusion and exclusion criteria for the Phase 3 studies?**

FDA Response: We do not object to your proposed clinical trials in patients with GA secondary to AMD, but request that you submit the charter for the proposed Data Safety Monitoring Board to the IND. See also our response to Question 5.

Please note that due to the formulation change from that used in the Phase 2 studies ((b) (4) powder for reconstitution) to the formulation now proposed for the Phase 3 studies (solution for injection, (b) (4) pH 5.0), we recommend that you re-evaluate the systemic PK exposure and estimate PK parameters for APL-2 following multiple IVT injections in a subset of 8 to 10 PK evaluable patients receiving APL-2 at 15 mg IVT once every month in one of the two proposed Phase 3 studies (Protocol APL2-303 or APL2-304). Please update the protocol to include the specific time points for PK sampling. We recommend that you submit your amended protocol for our review before initiating the study.

- 2. Does the Agency agree that a primary endpoint of mean rate of growth from baseline to month 12 in the square root of the total area of GA lesion(s) in the study eye (in mm per year) based on Fundus Autofluorescence (FAF) will support the indication: *treatment of patients with geographic atrophy (GA) secondary to AMD*?**

FDA Response: We agree with the mean rate of growth from baseline to month 12, measured as the total area of the GA lesion as the primary endpoint. We do not necessarily agree with using the square root of the total area. We note that the square root function for the total area of GA lesions is not the only mathematical model that could be used to account for the effect of baseline size on the difference in growth rates. We recommend that you evaluate the data upon completion of the trial to determine the best model to describe the total area growth over time.

- 3. Does the Agency agree that 12 months efficacy data from each of the Phase 3 studies at the to be marketed dose and dosing regimen is adequate to support NDA approval for the proposed indication?**

FDA Response:

The twelve-month efficacy data with the 24-month safety data with the marketed dose and dosing regimen is sufficient to file an NDA. NDA approval would be determined at the time the NDA submission is reviewed.

4. Does the Agency agree with the proposed statistical analyses for the primary and secondary efficacy endpoints?

FDA Response: *No. Your proposed primary method, longitudinal mixed-effects linear regression model, assumes a linear pattern for the efficacy outcome (square root of the total area of GA lesion) over the time course of 12 months for each treatment group. However, the submitted efficacy results of your Phase 2 study did not seem to support this assumption of linear pattern and we suggest that you consider other models.*

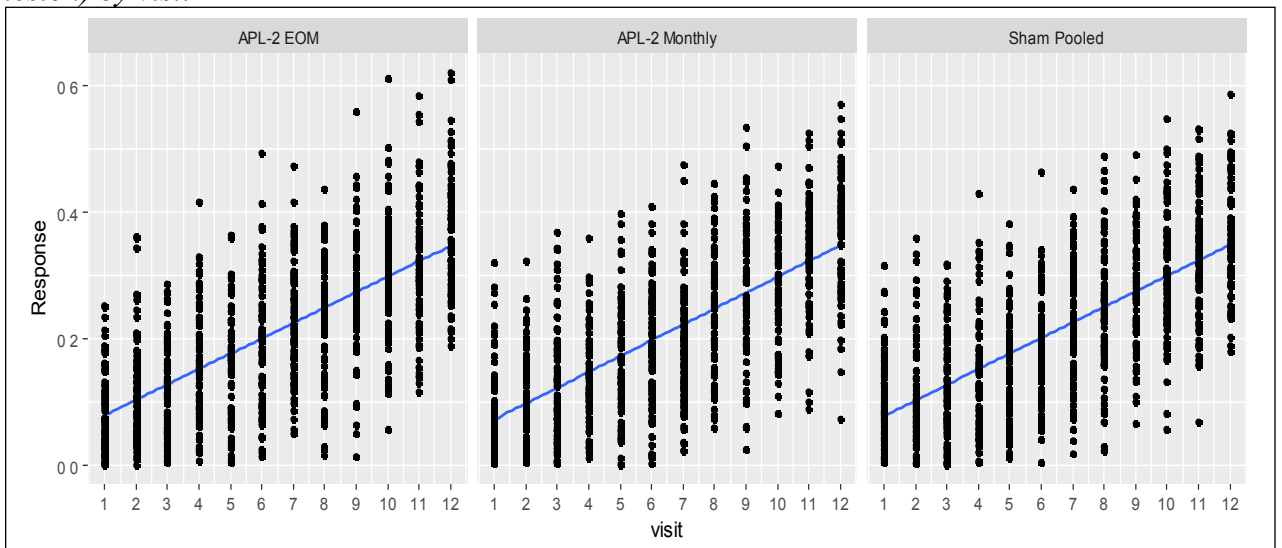
If you still consider using the longitudinal mixed-effects linear regression model as your primary method to estimate and compare the mean rate of growth, we have the following comments:

- *Please provide a justification for the linear assumption. Please also provide the following data from your Phase 2 study to aid evaluation of your proposed model and sample size calculation:*
 - a) *Two scatter plots with superimposed slopes (rates) based on the raw data (total area of GA lesion) and the change from baseline in the raw data (see Mock up Figure 1),*
 - b) *Two scatter plots with superimposed slopes (rates) based on the square root of total area of GA lesion and the change from baseline in the square root of total area of GA lesion (see Mock up Figure 1)*
 - c) *Figure 2 in your briefing package with superimposed slopes (rates) (see Mock up Figure 2).*
 - d) *Four summary tables as shown in Mock-up Table 1 for the following variables: raw total area of GA lesion, change from baseline in raw total area of GA lesion, square root of GA lesion, change from baseline in the square root of GA lesion*
- *The proposed longitudinal mixed-effects linear regression model is not clear. Please provide a detailed mathematics form of the model including all the fixed and random effects in the model and the variance-covariance structure. Please also include a sample SAS code.*
- *You stated on page 51 of the protocol that, “the model will estimate the subject level on-treatment slope and off-treatment slope with an on-off indicator variable, and these slopes will be compared.” Please clarify how these slopes will be compared.*

Additionally, you stated that, “the primary analysis, using the ITT data set will be performed on the on-treatment data only unless the comparison of the subject-level on-treatment and off-treatment slope indicates no difference, in which case all data will be used”. The primary analysis population should be pre-specified and not based on the result of any analyses. We recommend that the primary analysis be conducted on the ITT population including both on-treatment and off-treatment data.

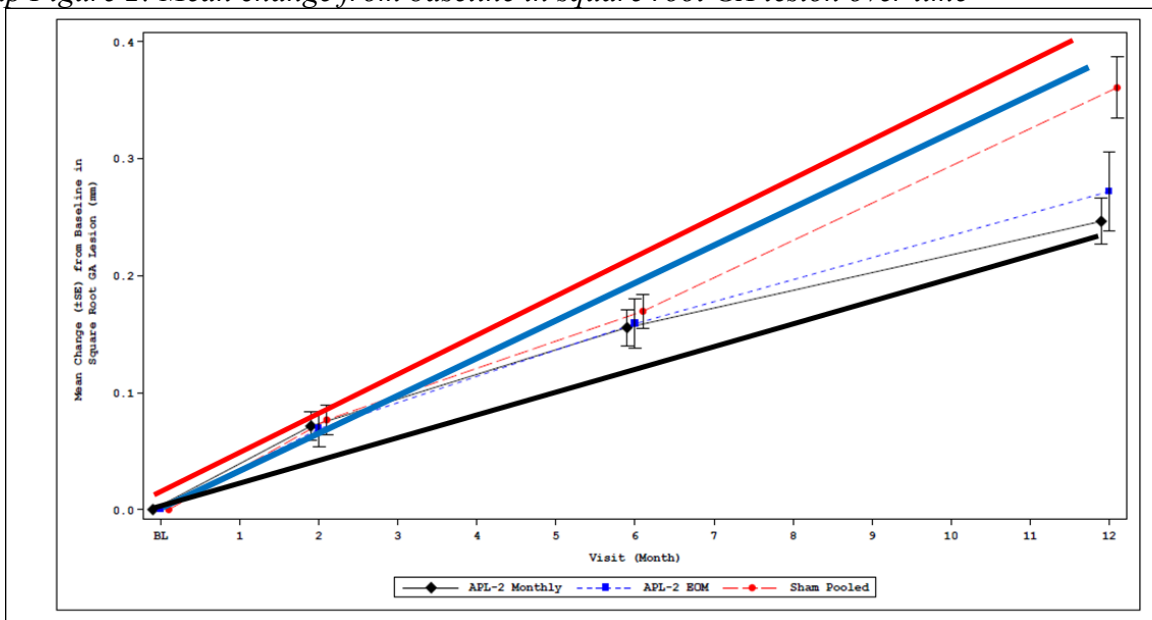
Regarding the missing data, you proposed to use a regression method of multiple imputation (MI) if more than 5% of data are missing. Please provide details on how this MI method will be incorporated to your primary analysis, including the details of the MI model and assumption on the missing mechanism. If your proposed MI method relies on the assumption of missing at random (MAR), we recommend sensitivity analyses be pre-specified to deal with the situation when MAR is violated.

Mock-up Figure 1: Scatter plot of raw data (or change from baseline in raw data or square root of the total GA lesion, or change from baseline in square root of total GA lesion) by visit



Note: you should include all available visits

Mock-up Figure 2: Mean change from baseline in square root GA lesion over time



Note: The red, blue, and black solid lines are the superimposed slopes (rates).

Mock-up Table 1: Summary statistics by visit

	AM	AMOE	Sham pooled
Baseline			
N			
Mean (SD)			
Median			
Min, Max			
Difference from sham pooled (95% CI)			NA
Month 1			
N			
Mean (SD)			
Median			
Min, Max			
Difference from sham pooled (95% CI)			NA
...			
Month 12			
N			
Mean (SD)			
Median			
Min, Max			NA
Estimated slope at Month 12 (SE)			
Estimated difference in slopes (95% CI)			NA

Note: you should include all available visits.

5. Does the Agency agree that the proposed safety database is adequate to support approval for the proposed indication?

FDA Response: Endothelial cell count examinations should be performed in one trial at baseline and at 6 months or more in a minimum of 100 eyes with the to-be-marketed dose and frequency of treatment; otherwise the proposed safety data base is acceptable. NDA approval would be determined at the time the complete NDA submission is reviewed.

NON-CLINICAL

The nonclinical package was developed in accordance with ICH M3(R2) guidance and in consideration of the specific safety considerations for PEGylated products. A summary of the proposed nonclinical pharmacology and toxicology program for the NDA is presented in Section 9. The nonclinical package proposed for the NDA includes:

- safety pharmacology
- pharmacokinetics
- ADME
- repeat dose chronic toxicology up to 6 and 9 months for primary ROA (IVT) in the monkey, and up to 6 and 9 months in the rabbit and monkey, respectively, for additional ROAs (SC and IV)
- genotoxicity
- studies designed to investigate the effects on reproductive indices

It is Apellis’s opinion that the proposed nonclinical package contains the necessary studies to fulfill the requirement for an NDA for APL-2 treatment of patients with GA.

6. Does the Agency agree that the proposed nonclinical pharmacology and toxicology program will fulfill the requirement for an NDA filing?

FDA Response: We agree. Provide a carcinogenicity study waiver request with the NDA. While a stand-alone fertility study is not expected, fertility should be addressed in the NDA. See below guidances for further reference.

*Addendum to ICH S6: Preclinical Safety Evaluation of Biotechnology -Derived Pharmaceuticals S6(R1)
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM194490.pdf>*

*M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073246.pdf>*

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

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

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

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

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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 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.

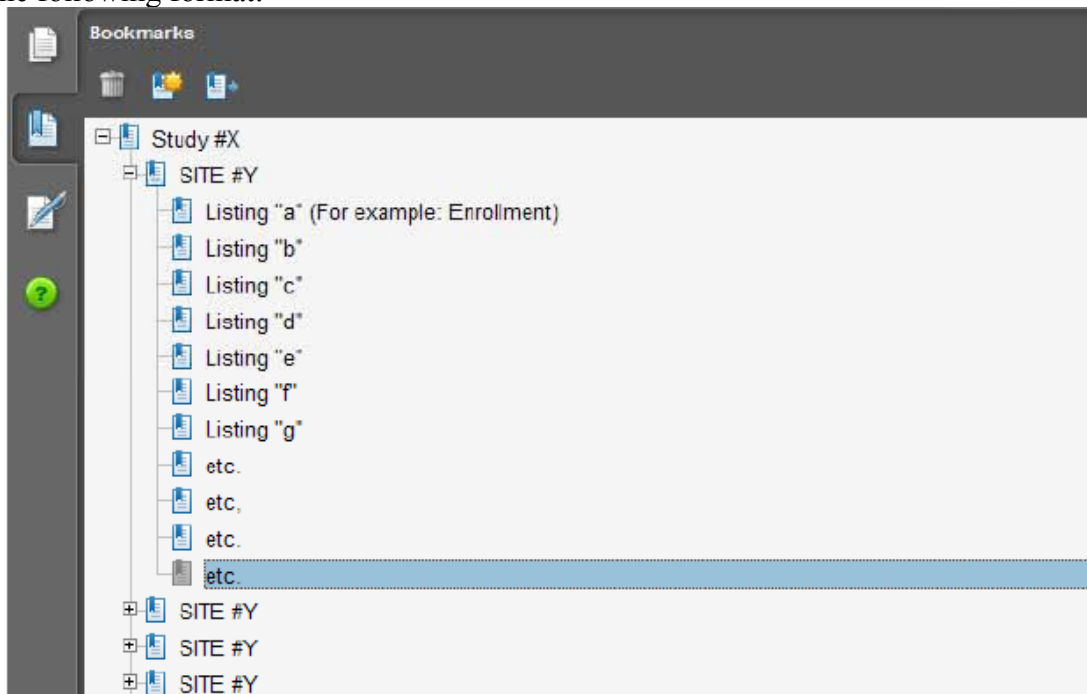
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued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



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

- 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.

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.

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

/s/

WENDY M STREIGHT
12/01/2017