CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215352Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135936

MEETING PRELIMINARY COMMENTS

Eyenovia, Inc.
Attention: Lee Kramm, MD, MSE
Vice President, Regulatory Affairs
295 Madison Avenue
Suite 2400
New York, NY 10017

Dear Dr. Kramm:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for phenylephrine and tropicamide ophthalmic solution ((b) (4) We also refer to your February 26, 2019, correspondence, requesting a meeting to seek feedback from FDA as Eyenovia plans an NDA submission. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 21, 2019 from 1:30pm – 2:30pm (EST)
Meeting Location: Teleconference

Application Number: 135936
Product Name: phenylephrine and tropicamide ophthalmic solution (b) (4)

Indication: to dilate the pupil
Sponsor Name: Eyenovia 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 May 21, 2019. 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.

DISCUSSION

Following, in **bold** font, are the questions in the April 18, 2019, Meeting Package. The FDA responses to these questions are in *italic* font.

NON-CLINICAL

1. **Based on the extensive clinical use of phenylephrine and tropicamide together, no issues to date identified with respect to impurities, and no reasons of concern identified in the clinical trials, there should be no concern regarding potential PK or toxicology interactions between active components. Does FDA agree that additional non-clinical testing is unnecessary for a future NDA for fixed combination Phenylephrine 2.5%/Tropicamide 1% microdose ophthalmic solution?**

FDA Response: We agree.

STERILIZATION

2. (b) (4)

FDA Response: We agree your limits for (b) (4) *are justified by the information provided. From a Microbiological perspective, the study appears reasonable, but the acceptability of the* (b) (4) *sterilization process validation is a marketing application review issue." In addition, please refer to FDA's 1994 "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" for additional information that is expected for a NDA submission to describe the microbiological control of your manufacturing process.*

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-documentation-sterilization-process-validation-applications-human-and-veterinary-drug

STABILITY

3. **Eyenovia is proposing a 24-month shelf-life for this drug product within the NDA. Eyenovia will update the filing as stability data become available. The manufacturing of this combination is straightforward:** (b) (4) **there is minimal risk identified.**

   Further, the solution stability of the individual APIs, phenylephrine and tropicamide, is proven, with U.S. commercial solutions of the individual APIs having an expiry of 2 years for phenylephrine (NDA 207926) and no apparent expiry on the labeling for tropicamide solutions. Outside of U.S., the combination product is commercially available and is labeled with a two year shelf-life.

   ICH Q1 suggests stability data from three primary lots with at least 12-month real time data to be submitted at NDA filing. These primary lots are commonly referred to as registration lots and later, either before or during NDA review, three validation lots are typically run. (b) (4) **sufficient for an NDA filing provided FDA agrees with the conclusion of the enclosed stability discussion?**

FDA Response: No, we do not agree with the proposed plan. The initial NDA submission should contain 6-month accelerated and at least 12-month long-term stability data for three primary drug product stability batches manufactured using the proposed commercial manufacturing process and packaged in the proposed commercial container closure system at the commercial manufacturing site. For detailed recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2) Guidance "Stability Testing of New Drug Substances and Products."

CLINICAL

4. **The final protocols and SAP's for the two Phase 3 studies (MIST-1 and MIST-2) are enclosed as part of this pre-NDA Briefing Document. Does FDA have recommendations for additional analyses to be performed or for the presentation and formatting of data in the marketing application in support of the proposed indications for use statement?**

FDA Response:

a) *As a supporting analysis, you plan to analyze the primary efficacy variable of the change from baseline in pupil diameter at 35 minutes using a reference-based multiple imputation (Table Number: Table 14.2.1.3). We recommend that similar analysis be performed for the secondary efficacy variable(s) of the proportion of eyes achieving pupil diameter of at least 6.00 mm by using the multiply imputed datasets.*

b) *For the analysis of the secondary efficacy variable of the proportion of eyes achieving pupil size of 6.0 mm or greater at 35 minutes, you proposed a generalized estimating equation (GEE) model where treatment comparison will be based on odds ratio. In addition to this analysis, we recommend that treatment comparison also be performed based on the difference in proportions.*

c) *Please provide the primary efficacy results and key safety summaries by the iris color strata.*

d) *In Section 7.0 (Table 4) of the Meeting Background Material, you outlined the proposed format for organizing the submission, including methods for presenting the data. We recommend that you create a folder named "datasets" in Module 5. Regarding the "datasets" folder structure, please consult Section 7 (Figure 1 and Table 2) of the Agency's 'Study Data Technical Conformance Guide' document (https://www.fda.gov/media/119807/download). We further recommend that you provide a 'reviewers-guide.pdf' document and a 'define.pdf' document for both the analysis and tabulation datasets of the two studies. The programming codes (preferably SAS codes) used to create the analysis datasets and the efficacy and safety tables should also be provided.*

505(B)(2) Regulatory Pathway

5. **The proposed 505(b)(2) bridging information was provided within the respective sections of IND 135936. Does FDA have any specific recommendations for the general organization of the NDA as well as for the content and layout of the 505(b)(2) bridging information to be provided in the marketing application?**

FDA Response:

None at this time, the organization appears appropriate.

Labeling

6. **Are the content and layout for the draft product labels (affixed to microdose dispenser cartridge, base, and box) acceptable?**

FDA Response: If [redacted] (b) (4) *are part of the proposed trade names, the established name should be revised on the carton labels to a prominence one-half of whatever is most prominent on the label. Refer to 21 CFR 201.10(g)(2).*

[redacted] (b) (4) *should be deleted.*

Final review of the product labeling will be completed at the time of NDA review.

Additional Comments:

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

1 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

2 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

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*.

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[3] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[4]

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

If you intend to rely on literature or other studies for which you have no right of

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.regulations.gov

reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

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

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

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

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

In addition to identifying the source of supporting information in your annotated labeling,

we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

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

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

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/

LOIS A ALMOZA
05/15/2019 07:51:29 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 135936

MEETING PRELIMINARY COMMENTS

Eyenovia Inc.
c/o ClinReg Consulting Services, Inc.
Attention: Lee Kramm, M.D., M.S.E.
Regulatory Consultant
501 Fifth Avenue, Suite 1404
New York, NY 10017

Dear Dr. Kramm:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Tropicamide 1%-Phenylephrine 2.5% μD.

We also refer to your June 15, 2017, correspondence, received June 16, 2017, requesting a meeting to seek guidance from FDA on the adequacy of the Phase 3 clinical development plan in support of an NDA for PHEN/TROP μD.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: September 18, 2017 from 3:00pm – 4:00pm (EST)
Meeting Location: Teleconference

Application Number: 135936
Product Name: Tropicamide 1%-Phenylephrine 2.5% μD
Indication: to dilate the pupil
Sponsor/Applicant Name: Eyenovia 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 September 18, 2017. 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.

DISCUSSION

Following, in **bold font**, are the questions in the August 16, 2017, Meeting Package. The FDA responses to these questions are in *italic* font.

Questions

505(B)(2) REGULATORY PATHWAY

1. **Eyenovia intends to pursue a 505(b)(2) regulatory pathway for PHEN/TROP µD, to allow reference to be made to the publicly available nonclinical testing available for the two components. The ocular safety of tropicamide and phenylephrine are well established, with a long history of safe use. Additionally, the formulation of topical tropicamide and phenylephrine in PHEN/TROP µD is identical or very similar to the commercial products and delivered in a smaller total dose, with inactive ingredients known to be safe when used in ocular formulations. Does FDA agree that the proposed plan to bridge publicly available information for tropicamide and phenylephrine within the 505(b)(2) construct is adequate to support the planned Phase 3 IND clinical trials? If not, what additional testing should be conducted to support the IND clinical trials and a future NDA?**

Agency Response: Yes, based on the extensive clinical use of phenylephrine and tropicamide together, we agree that the proposed plan to bridge publicly available information within the 505(b)(2) construct for the clinical trials is acceptable.

Regarding the question about additional testing, it is not anticipated that additional nonclinical studies will be needed, provided there are no issues with excipients or impurities that will need nonclinical qualification, and no reasons of concern arise in the clinical trials. You should, however, provide a rationale in the NDA to support a lack of concern regarding potential PK or toxicology interactions between active components, based on recommendations contained in the Guidance to Industry on "Nonclinical Safety Evaluation of Drug or Biologic Combinations" at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079243.pdf . The adequacy of the data provided to support the NDA will be a review issue.

Additional recommendations:

a. *You may not rely on the data and information in the NDA for the listed drug(s); you can rely only on the finding of safety and effectiveness (captured in the product labeling). Note that FDA discipline reviews and summary basis of approvals (SBAs) cannot be relied-upon in a 505(b)(2) NDA application.*

b. *All nonclinical elements should be provided, either directly (original studies or published literature) or by relying on the FDA's findings of safety and effectiveness for a listed drug. If literature is being relied upon to support the NDA, include an integrated summary of all published nonclinical literature being relied upon and a copy of all publications cited. The nonclinical summary is typically organized to address each of the nonclinical elements (e.g. pharmacology, pharmacokinetics, ocular*

toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.). See Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals for further information regarding required nonclinical elements.

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf)

c. *If you intend to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate. You should establish an adequate "bridge" (e.g., via comparative pharmacokinetic/exposure data) between your proposed drug product and the listed drug. If exposure levels using your proposed formulation are less than or equal to that of the listed drug (at approved dose), then reliance upon the listed drug is considered scientifically justified.*

d. *Please also identify any listed drug(s) described in the published literature (e.g., trade name(s)). Reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s).*

e. *Impurity specifications that exceed qualification limits specified in the ICHQ3 guidances should be adequately qualified and the supporting safety data should be provided in the NDA submission. Ensure that ocular and systemic safety are addressed.*

MANUFACTURING SCALE/FORMULATION AND FILL METHODS

2. **The manufacture of the Eyenovia Tropicamide (1%) -- Phenylephrine (2.5%) sterile ophthalmic solution GMP Drug Product batches will be produced under th** (b) (4) **The primary container will be a standard 2 mL vial with a container closure system composed of a stopper and crimp seal. The Company plans to** (b) (4)

Is this approach, (b) (4) **without having to conduct an additional clinical study? What form of NDA**

supplement, if necessary, is needed [redacted] (b) (4) after approval of the NDA?

Agency Response: The pilot batch can be used for clinical supplies. We suggest you submit a comparability protocol to cover the manufacturing process changes you intend to implement in the NDA submission. Changing from [redacted] (b) (4) post-approval of the NDA will require filing of a Prior Approval Supplement (PAS). The PAS should include the supporting [redacted] (b) (4) validation data for the [redacted] (b) (4) process. For more information regarding submission documentations, please refer to both the 1994 Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products and the 2004 Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.

CLINICAL

3. **Based on the known safety of the components, are the study designs for the two Phase 3 clinical studies adequate to support a future NDA application for PHEN/TROP µD for the proposed indications for use? Does FDA have additional recommendations regarding the proposed study designs with respect to the control arms, enrollment criteria, statistical plans, etc.?**

Agency Response: It is recommended that the primary efficacy endpoint be defined as the proportion of eyes that achieve a pupil size of ≥ 6 mm under lighting consistent with an indirect ophthalmoscope, as measured by digital pupillometry.

The enrollment criteria should not limit subjects to those over the age of 18 since pupil dilation is required for both adult and pediatric patients.

Safety and efficacy analyses should also account for differences in iris color.

ADDITIONAL AGENCY COMMENTS

In the second Phase 3 study, you proposed 2-treatment 3-period crossover design (ABB or BAA; where A is the fixed combination and B is the placebo control).

a. *Please clarify why this design choice is appropriate to address the trial objective.*
b. *Study drugs will be administered in the study at the two scheduled visits; however, it is not clear when treatment at period 3 will be administered. Please clarify.*

The primary efficacy analyses methods are not pre-specified in both study synopses. Please specify the primary efficacy analyses methods including the analyses populations, missing data handling methods, and multiplicity adjustment procedures when the full protocols are submitted for review.

LABELING

4. Is the content and layout for the draft product labels [redacted] (b) (4) acceptable for use in the phase 3 program and in a future NDA for PHEN/TROP µD?

Agency Response

No. See 21 CFR 312.6 - Labeling of an investigational new drug: (a) "The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." This regulation also applies to Phase 3 trials.

Final labeling is a review issue discussed after submission of a complete application.

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 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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).

505(b)(2) REGULATORY PATHWAY

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

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

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

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

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

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

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

application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

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

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

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

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/

LOIS A ALMOZA
09/12/2017