CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217836Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131464

MEETING MINUTES

ORASIS Pharmaceuticals, Ltd
(b) (4)

Dear Mr. (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CSF-1 Ophthalmic Solution. We also refer to the meeting between representatives of your firm and the FDA on August 17, 2022, requesting a meeting to discuss results from two Phase 3 pivotal studies in support of upcoming NDA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at (301) 796-1002.

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:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 17, 2022; 3:00-4:00 PM EDT
Meeting Location:	Teleconference
Application Number:	IND 131464
Product Name:	CSF-1 Ophthalmic Solution
Indication:	treatment of presbyopia
Sponsor Name:	ORASIS Pharmaceuticals, Ltd
Regulatory Pathway:	505(b)(1)

FDA ATTENDEES

Wiley Chambers, MD	Director, Division of Ophthalmology (DO)
William Boyd, MD	Deputy Director, DO
Rhea Lloyd, MD	Clinical Team Leader, DO
Sonal Wadhwa, MD	Clinical Reviewer, DO
Mukesh Summan, PhD	Director, Division of Pharmacology and Toxicology for Rare Diseases, Pediatrics, Urologic & Reproductive Medicine/Specialty Medicine (ORDPURM/DPTRDPURM)
Erin Ruhland, PhD	Pharmacology/Toxicology Reviewer, ORDPURM/DPTRDPURM
Ping Ji, PhD	Team Leader, Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)
Da Zhang, PhD	Clinical Pharmacology Reviewer, OTS/OCP/DIIP
Greg Soon, PhD	Statistics Team Leader, Office of Biometrics/Division of Biometrics IV (OB/DBIV)
Solomon Chefo, PhD	Statistician, OTS/OB/DBIV

SPONSOR ATTENDEES

ORASIS Pharmaceuticals, Ltd

Elad Kedar	CEO
Ron Neuman	Chief Medical Officer
Ilan Rubin	Director Quality Assurance
Iris Meisner	Head of Regulatory Affairs

(b) (4)

1.0 BACKGROUND

The meeting package, including questions, was submitted on July 15, 2022. After review of the meeting package, FDA sent preliminary comments to the Sponsor on August 10, 2022. For the August 17, 2022 meeting, ORASIS requested further discussion of their clarifying questions 4, 4a and 4b from an official submission dated August 15, 2022. The questions are provided in bold print. FDA's responses to the questions are provided in italic font and the meeting discussion is in normal font.

2.0 DISCUSSION

CMC:

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Nonclinical:

Question 2

As part of the Type C meeting (August 25, 2021), Orasis presented a proposed nonclinical testing strategy to deliver the relevant nonclinical safety data to support the 505(b)(1) NDA pathway (Appendix 1). This strategy was considered acceptable to the Agency. It was also noted that "*should Orasis obtain RoR to long term safety pilocarpine study(ies) or any other nonclinical studies, there would be no need to repeat these studies.*"

Orasis is conducting the 2 repeat ocular dose studies as described to support the safety of the CSF-1 formulation (a 6-month repeat ocular dose/local tolerance study in rabbits, a 1-month repeat ocular dose impurity qualification in rabbits),

an ocular distribution pharmacokinetic (PK) study after a single ocular dose in rabbits, and an in vitro hERG assay. Orasis has also secured RoR to Salagen's NDA 020237, and thus, will refer to study reports (GLP) included in the Salagen NDA, for the general safety of pilocarpine. These include repeat oral dose studies in rats (13 weeks) and dogs (26 weeks), a full battery of genotoxicity studies, carcinogenicity studies in mice and rats, and a battery of reproductive toxicity studies (fertility and early embryonic development in rats, embryofetal toxicity studies in rats and rabbits, and pre- and postnatal development in rats).

Does the Agency agree that the proposed nonclinical safety package, with systemic repeat dose studies (13-week day rat study and 26-week dog study), genotoxicity studies, carcinogenicity studies and reproductive and developmental toxicity studies, obtained by RoR in lieu of testing, together with the ocular animal studies conducted with CSF-1, is sufficient to support the 505(b)(1) NDA pathway?

Agency Response: With the right of reference to NDA 20-237, the proposed nonclinical safety package is expected to be sufficient for filing of the NDA. Approval of the NDA is a review issue.

No discussion

Clinical:

Question 3
Orasis plans to include in the ISE, an analysis with the integrated data sets of both pivotal studies (NEAR-1 and NEAR-2) of all primary, key secondary, other secondary endpoints and certain exploratory endpoints (e.g., pupillometry). In addition, sub-group analyses, described in the Sponsor's Position will be included. Does FDA agree with this plan?

Agency Response: Overall efficacy results and subgroup analyses should be summarized and described separately for all individual studies. As supporting analysis, we have no objection to your proposed ISE plan.

No discussion

Clinical Safety:

Question 4
Orasis proposes to submit its NDA for CSF-1, utilizing results from its own clinical studies consisting of data for 477 subjects treated with CSF-1 for various durations. In addition, the entire clinical safety data of Salagen NDA 020237 including 245 patients, treated with oral pilocarpine for one year, will support the requirements for long-term (1 year) clinical safety data.

Does FDA agree that the safety database size is adequate to support the NDA submission under the 505(b)(1) pathway?

Agency Response: Agree.

Meeting Discussion:
FDA confirmed the adequacy of the planned safety database, including the plan for shortening the ongoing 21- 150-0005 safety study (i.e. shortening the study duration to a minimum of 6 weeks for cohort 1 for at least 100 subjects on CSF-1 and 50 on vehicle, removal of cohort 2 and removal of specular microscopy). FDA also agreed that the safety assessments currently included in 21-150-0005 (excluding specular microscopy) are adequate. FDA stated that the right of reference (RoR) to the Salagen NDA together with the planned safety database appear to fulfil the safety requirements to support an NDA filing for CSF-1 under the 505(b)(1) pathway.

Orasis confirmed that the CSRs of the phase 3 pivotal studies (NEAR-1 and NEAR-2), providing the efficacy and safety data for CSF-1, will be complete and submitted with the initial NDA submission. FDA agreed with the submission of masked interim safety data from the ongoing study 21-150-0005 at the time of NDA submission. The Day 120 Safety Update will include the full CSR of Study 21-150-0005, the datasets and updated ISS tables integrating the proposed safety data together with the pivotal studies (NEAR-1 and NEAR-2).

No further recommendations or comments were provided.

Labeling:

Question 5
Utilizing its right to reference Salagen's NDA and based on Salagen's approved label (Salagen® USPI 2022), updated to current labeling requirements, Orasis has drafted language for sections 8.1 Pregnancy, and 8.2 Lactation, of its label provided below. Orasis seeks FDA's feedback on the proposed language to be submitted as a part of the proposed label in the NDA. Additionally, Orasis seeks FDA's guidance and suggested class language if the provided language is not adequate.

Agency Response: Labeling is a review issue, and this question cannot be definitively answered until an NDA is submitted and reviewed.

No discussion

Question 6
Utilizing its right to reference Salagen's NDA and based on Salagen's approved label (Salagen® USPI 2022), Orasis has drafted language for section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, of its label provided below.

Orasis seeks FDA's feedback on the proposed language to be submitted as a part of the proposed label in the NDA. Additionally, Orasis seeks FDA's guidance and suggested class language if the provided language is not adequate.

Agency Response: *See response to Question #5.*

No discussion

NDA Format:

Question 7
Orasis proposes to include the audited draft report of the 6-month repeat ocular dose toxicity study in rabbits under Local Tolerance-Section 4.2.3.6, at the time of submission, and provide the final report and dataset in SEND format as a part of the 120-day safety update.

Does FDA agree with this approach?

Agency Response: *We agree.*

No discussion

Question 8
Orasis plans to submit the data obtained under RoR to Salagen's NDA 020237, as accurate summaries discussed in Module 2, without resubmission of study reports, post text tables and case report forms.

Does FDA agree with this approach?

Agency Response: Acceptable.

No discussion

Attachment:

- ORASIS Pharmaceuticals, Ltd Meeting Discussion Points

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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
09/07/2022 08:09:10 PM

U.S. FOOD & DRUG ADMINISTRATION

IND 131464

MEETING MINUTES

ORASIS Pharmaceuticals, Ltd c/o (b) (4)
(b) (4)

Dear Mr. (b) (4)

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CSF-1 Ophthalmic Solution. We also refer to the meeting between representatives of your firm and the FDA on March 9, 2020 to present to the Agency plans for Phase 3 protocol design, non-clinical development, and CMC formulation development.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: March 9, 2020, 2:00-3:00 PM EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: IND 131464
Product Name: CSF-1 Ophthalmic Solution
Indication: (b) (4) (b) (4) presbyopia

Sponsor/Applicant Name: ORASIS Pharmaceuticals, Ltd

Meeting Chair: Wiley Chambers, MD
Meeting Recorder: Jacquelyn Smith, MA

FDA ATTENDEES:

Wiley Chambers, MD	Deputy Director, Division of Ophthalmology (DO)
William Boyd, MD	Medical Team Leader, DO
Sonal Wadhwa, MD	Medical Officer, DO
Chunchun Zhang, PhD	Chemistry Team Lead, OPQ/ONDP/DNDPI/NDPB3
Dustin Thomas, PhD	Microbiologist, OPQ/OPMA/DMAI/MAB1
Greg Soon, PhD	Statistics Team Leader, OTS/OB/DBIV
Yunfan Deng, PhD	Statistician, OTS/OB/DBIV
Jacquelyn Smith, MA	Senior Project Manager, ORO/DRO

ORASIS Pharmaceuticals, Ltd

Elad Kedar	Head of Pharmaceutical Development and Manufacturing
(b) (4)	VP, Posterior Segment Senior Vice President Senior VP Quality, CMC and Regulatory Manager, Regulatory Writing

Statistics and Data Corporation

(b) (4) (b) (4)

1.0 BACKGROUND

In a November 7, 2019 submission, ORASIS requested a meeting and subsequently submitted their briefing package. The meeting was granted, the briefing package was reviewed, and the Agency sent preliminary responses to questions on March 4, 2020. ORASIS' questions are in **bold** font, FDA's preliminary responses are in *italic* font and the meeting discussion is in regular font. The questions requiring further discussion are 5, 8, 9, 11a, and 17. The discussion of those questions are included below.

2.0 DISCUSSION

Chemistry, Manufacturing, and Controls

(b) (4)

Non-Clinical

2. **Pilocarpine ophthalmic solution is an FDA approved drug for decades. It has been extensively used at concentrations up to 4% with a dosing regimen up to 4 times daily for chronic conditions (such as Open-Angle Glaucoma or Ocular Hypertension). This approved dosage is up to 20 times higher than the dosage to be used in the proposed CSF-1 clinical program (pilocarpine HCl 0.4%, BID). In addition, the current formulation of CSF-1 has been tested in one of the study arms of the clinical Phase 2b study.**

   Does the Agency agree that no additional non-clinical studies are required with the current CSF-1 (pilocarpine HCl 0.4%) formulation to:

   a) Proceed with the Phase 3 study?

   Agency Response: We agree.

   b) Submit an NDA?

   Agency Response: We agree, presuming adequate justification is provided in the NDA for any impurity specification which exceeds Agency qualification thresholds. A final determination regarding the adequacy of the nonclinical data to support your NDA will be made based on review of full study reports provided in the NDA submission.

3. **The Sponsor is investigating the possibility to adjust the current formulation of CSF-1 (pilocarpine HCl 0.4%) by** (b) (4) **The Sponsor is evaluating whether the** (b) (4) **present in the current CSF-1 formulation is required as a** (b) (4) **. (see Section 11.1.6).**

   Because (b) (4) **of the drug product, there are no safety concerns if the sponsor chooses** 11 Page(s) has been **while succeeding** (b) (4) **and meeting product specifications.**

   In the Sponsor's opinion, a non-clinical study with the adjusted CSF-1 formulation (pilocarpine 0.4% (b) (4) **) is not required, to proceed to the Phase 3 study, should the Sponsor decide to move forward with this formulation.**
   Does the Agency agree?

   Agency Response: We agree.

Clinical

4. **Given the extensive use of pilocarpine ophthalmic solutions at much higher concentrations (up to 4%) and the pharmacokinetic study mentioned in the label of Isopto® Carpine (NDA#200890, approved label 2010) (see section 11.3.1), does the Agency agree that no clinical Pharmacokinetics (PK) study with CSF-1 (0.4% pilocarpine) to evaluate systemic exposure, is required to support NDA submission?**

   Supporting the following questions 5 to 17, a summary of the proposed clinical development plan is included in Section 11.3 of this briefing document, and a full protocol for the proposed Phase 3 clinical trial is included in Appendix 1.

   Agency Response: No, we do not agree. An estimation of the systemic PK exposure of pilocarpine is needed to establish a scientific bridge to the reference product. An adequate attempt to develop a sensitive assay method should be made to measure low concentrations of pilocarpine.

5. **The proposed primary efficacy endpoint for this study is the percentage of subjects with ≥3-line improvement from baseline in BCVA score (40 cm) at Day 15, one-hour post AM dose administration. This is the identical primary end-point as used in the phase 2b study. Does the Agency agree with the proposed primary endpoint for the pivotal Phase 3 study?**

   Agency Response: The primary endpoint is acceptable provided that the evaluation is performed with the best correction for distance visual acuity and there is no change in distance visual acuity.

   Meeting Discussion (Questions 5 and 8)
   The Sponsor clarified that a manifest refraction would be performed at Visit 1 at 4m using an ETDRS refraction chart. The 4m refraction obtained will be placed into trial frames and used for all visual acuity tests (i.e., 4m ETDRS, 4m low luminance ETDRS and 40cm near acuity testing) during the study period (i.e., baseline and all post-treatment assessments). The Agency agreed that this was acceptable.

   The Sponsor also clarified that the near visual acuity is measured using a 40cm 'ETDRS-like' chart from Precision Vision. Per the Sponsor, the 40cm Precision Vision chart uses the same letter and line spacing as the ETDRS chart, only calibrated in size for testing at 40cm. Similar to the 4m chart, the Precision Vision 40cm chart is placed in light box creating retroillumination for testing. The Agency agreed that this test was acceptable for the near visual acuity endpoint. The Agency requested the Sponsor use a different description of the chart than 'ETDRS' as the 'ETDRS' chart typically refers to 4m testing. It was agreed that the

40cm charts would be referred to as '40cm Precision Vision chart' in future versions of the protocol and BCVA manual.

The Agency clarified that in order to be considered a success, a subject must gain ≥3-lines (i.e., halving of visual angle) in best distance corrected near VA at 40cm AND also not lose ≥5 letters in best distance corrected VA at 4m.

6. **Does the Agency agree that 4 weeks of dosing with CSF-1 is appropriate to assess the safety and efficacy of this product indicated for the (b) (4) of presbyopia?**

Agency Response: Yes.

7. **Does the Agency agree that the Sponsors evaluation of the exploratory endpoint of tachyphylaxis at Week 4 is sufficient?**

Agency Response: Acceptable.

8. **Does the Agency agree that the BCVA manual located in Appendix 4 is appropriate to evaluate the primary endpoint variable (BCVA at 40 cm)?**

Agency Response: No. Evaluations must be performed with using the distance (4 meter) corrected visual acuity and also include an evaluation of the distance visual acuity.

Meeting Discussion
See discussion under question 5.

9. **Does the Agency agree that the Low-Luminance Distance Visual Acuity procedure described in the BCVA manual is sufficient to evaluate the safety issues related to pupil miosis?**

Agency Response: No. Pupil miosis will be assumed to reduce visual function in lower light conditions.

Meeting Discussion
The Agency stated that loss of low luminance visual function is a labeling issue, and drugs that induce pupil miosis would carry a 'Poor Illumination' label similar to Isopto Carpine even if results are obtained in the Phase 3 studies that show no loss of Low-Luminance BDCVA.

10. **The FDA has previously approved ophthalmic solutions with pilocarpine hydrochloride at dosages up to 4.0%, 4 times daily (equivalent to 20 times the dosage in CSF-1). In addition, all excipients in CSF-1 are common**

(b) (4)
(b) (4)

a. **Does the Agency agree that the planned duration of 4 weeks of dosing with CSF-1, completed with data from the literature on long term use of ocular pilocarpine, is sufficient to support the long term safety of CSF-1?**
b. **Does the Agency agree that a chronic safety study with CSF-1 is not required for NDA approval of CSF-1?**

Agency Response: Yes.

11. **The results of the Phase 2b factorial study indicated that the CSF-1 formulation with 0.4% pilocarpine hydrochloride, showed a statistically significant (evaluated at a 2-sided alpha =0.025 using Bonferroni correction for two primary endpoints) higher effect than diclofenac alone (0.006%) in the temporary correction of presbyopia as evidenced by improved BCVA ≥3 lines at 40 cm, 1-hour post-dose at Visit 4, p=0.0002, in the Per Protocol (PP) population, and P=0.0008 in the intent-to-treat (ITT) population both with observed data only. The clear statistical significance was further and consistently confirmed by secondary statistical analysis as well as the exploratory analysis and sensitivity analyses (including multiple imputations of missing data and imputing missing as failures), of the primary efficacy endpoint.**

a. **Does the Agency agree that the Phase 2b factorial study comparing the efficacy and safety of the combination (pilocarpine [0.2%, 0.4%] + diclofenac 0.006%) and pilocarpine alone ([0.2%, 0.4%] versus diclofenac (0.006%) alone, represents an adequate and well-controlled study and may be considered as one of the two required adequate and well-controlled trials to support an NDA submission?**

Agency Response: You have only provided a summary of the study results. We would need to review the entire CSR (clinical study report) to determine the acceptability of the Phase 2b study.

Meeting Discussion (11a)
The Agency agreed to review the CSR and provide feedback on whether the Phase 2b could be considered an adequate and well-controlled study.

b. **If yes, and assuming that the proposed Phase 3 study is successful, does the Agency agree that the Sponsor will have satisfied the efficacy and safety requirements for the NDA submission?**

Agency Response: Acceptability of an NDA can only be determined after review of a complete NDA.

12. Does the Agency have any other comments or recommendations on the clinical development plan or the proposed clinical protocol?

Agency Response: No additional comments.

Statistics

13. Does the Agency agree with the proposed sample size, alpha level, and powering parameters proposed for the Phase 3 efficacy study?
Agency Response: The proposal appears acceptable.

14. Would the agency provide feedback on our primary estimand and strategy for handling intercurrent events?

Agency Response: See Agency comment for Question 8 regarding the primary efficacy endpoint.

Your proposed primary estimand is as follows:

- *Population: subjects with Presbyopia defined through enrollment criteria*
- *Endpoint:*
  - *Response defined as a ≥ 3-line (15-letter) gain, from baseline, in BCVA at 40 cm at Visit 3, 1-hour post-treatment*
- *Intercurrent event:*
  - *Discontinuation of study drug and non-optimal compliance will be ignored [treatment policy strategy].*
  - *Withdrawal due to lack of efficacy or adverse events: missing data will be singly imputed as failure [hypothetical strategy].*
  - *Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse events: missing data will be imputed employing Multiple Imputation (MI) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].*
- *Population-level summary:*
  - *The difference, between study eyes treated with pilocarpine hydrochloride and study eyes treated with vehicle, in the percentage of study eyes with a ≥ 3-line (15-letter) improvement from baseline in BCVA at 40 cm on Day 15, 1-hour post-treatment.*

In addition, as part of your sensitivity analyses, you propose that the primary efficacy variable will be analyzed using the FAS with all missing data imputed as failures.

The above strategy for handling intercurrent events appears acceptable. Additionally, we recommend you take all possible measures to minimize missing data by following and conducting efficacy and safety evaluation for all treated patients throughout the study.

15. The Sponsor plans to assess onset of duration and duration of action as separate secondary endpoints. Theses endpoints are as follows:

1. **Onset of Action: Percentage of subjects with a ≥ 3-line (15-letter) gain in BCVA at 40 cm at Visit 3, 20 minutes post-treatment**
2. **Duration of Action: Percentage of subjects with a ≥ 3-line (15-letter) gain in BCVA at 40 cm at Visit 3 tested in the following hierarchical manner:**
   - **2 hours post-treatment**
   - **3 hours post-treatment**
   - **4 hours post-treatment**

The Sponsor proposes that secondary endpoint #1 is a reflection of onset of action of CSF-1, and endpoint #2 is a reflection of duration of action. Does the Agency agree that the Sponsor may evaluate each secondary endpoint with a two-sided alpha level of 0.05, where for duration of action, the time points will be evaluated in a hierarchical order?

Agency Response: See Agency comment for Question 8 regarding the primary efficacy endpoint. From statistical perspective, the proposed hierarchical strategy of controlling Type I error rate is acceptable.

16. Would the agency provide feedback on our proposed primary analysis methodology?

Agency Response: As part of the sensitivity analyses, for both primary and secondary efficacy endpoints, we recommend that you estimate and test the difference in the proportion of responders between the treatment groups using chi-square test while treating all missing data as treatment failures.

17. The Sponsor is considering assessing the sustained duration of action of CSF-1 as an exploratory endpoint. A description of the efficacy analysis can be found in Section 11.5.3. Would the agency provide feedback on the acceptability of using sustained ≥ 3-line (15- letters) improvement from baseline BCVA at 40 cm to each time point (2, 3- and 4- hours post-treatment) as the primary assessment of duration of action? A subject will be considered to have a sustained response at a time point if the subject had a response at that time point as well as all earlier time points (back to 1 hour) at the visit.

Agency Response: See Agency comment for Question 8 regarding the primary efficacy endpoint. Since the 2-, 3-, 4-hour time points at Visit 3 (Day 15) will be tested as the secondary analyses, our understanding is that you plan to test Visit 4 (Day 29) at 2-, 3-, 4-hour time point in addition to 2-, 3-, 4-hour time points at Visit 3 to assess the duration of action. If so, please clarify your strategy for controlling Type I error rate for the additional endpoints tested at Visit 4 (Day 29).

Meeting Discussion
The Agency agreed that there were multiple approachs for demonstrating the duration of action but the Type I error must be appropriately controlled and defined in the statistical analysis plan. The Agency also stated that if the Sponsor chooses to use the sustained ≥ 3-line (15- letters) improvement methodology, then the observed outcomes will be evaluated for consistency across the time points.

3.0 OTHER COMMENTS

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 (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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application

review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product

development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILEY A CHAMBERS
04/05/2020 10:00:16 PM