CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214510Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 102233

MEETING MINUTES

Sol-Gel Technologies, Ltd.
c/o B&H Consulting Services, Inc.
Attention: Elizabeth N. Dupras, RAC
Senior Director, Regulatory Affairs
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Ms. Dupras:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for benzoyl peroxide cream, 5%.

We also refer to the meeting between representatives of your firm and the FDA on February 05, 2020. The purpose of the meeting was to discuss the format and content of proposed 505(b)(2) NDA for submission benzoyl peroxide cream.

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 Barbara Gould, Chief, Project Management Staff at 301 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor Agenda and Handout

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 05, 2020 at 1:30 PM
Meeting Location: Bldg. 22, Conference Room 1315

Application Number: IND 102233
Product Name: benzoyl peroxide cream, 5%

Proposed Indication: For the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older
Sponsor Name: Sol-Gel Technologies, Ltd.

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Barbara Gould

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
Hamid Shafiei, PhD, Quality Assessment Lead, DNDP II, NDPB V
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
David Nartey, PharmD, Regulatory Health Project Manager, DDDP
Kimberle P. Searcy, MPH, Regulatory Health Project Manager, DDDP
Qianyiren Song, PharmD, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Ofer Toledano, Ph.D., Vice President Research and Development, Sol-Gel Technologies, Ltd.
Ofra Levy Hacham, Ph.D., Vice President Clinical and Regulatory Affairs, Sol-Gel Technologies Ltd.
Miri Nadler Milbauer, Ph.D., MBA, Regulatory Affairs Manager, Sol-Gel Technologies Ltd.
Michal Yaron, B.Sc., Regulatory Affairs Manager, Sol-Gel Technologies Ltd.
Tali Amir-Azulay, M.A., Biometrics and Clinical Operations Manager, Sol-Gel Technologies Ltd.

Birju Patel, M.S., Senior Regulatory Affairs Project Manager, B&H Consulting Services, Inc. (Regulatory Consultant)
Elizabeth N. Dupras, RAC, Senior Director, Regulatory Affairs, B&H Consulting Services, Inc. (US Agent and Regulatory Consultant)

1.0 BACKGROUND

The purpose of this meeting is to discuss the format and content of proposed 505(b)(2) NDA for submission benzoyl peroxide cream.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 11/05/2019 Final Written Response
- 03/05/2019 Type C Guidance (CMC) Meeting
- 11/29/2017 End of Phase 2 Meeting

We have sent the following correspondences:

- 03/05/2019 Special Protocol Modification – No Agreement
- 09/09/2018 Pediatric Study Plan – Initial Agreement
- 08/16/2018 Advice Letter
- 07/10/2018 Pediatric Study Plan – Written Response
- 04/05/2018 Special Protocol – Agreement
- 02/15/2018 Pediatric Study Plan – Incomplete
- 02/14/2018 Special Protocol – Request Denied
- 01/12/2018 Proprietary Name Granted
- 05/01/2012 Advice/Information Request
- 04/22/2010 Advice/Information Request
- 10/21/2009 Advice/Information Request

2.0 DISCUSSION

2.1. Regulatory

Question 1:
Does the Agency agree with the organization of the eCTD?

FDA Response to Question 1:
In general, the proposed organization of the eCTD (Attachment 1) appears reasonable.

In addition, include a discussion of the following in your Summary of Clinical Safety 2.7.4 (or the Clinical Overview):

- Risk and benefit assessment of your drug product compared to other marketed drug products for the same indication.
- Local safety findings across trials in your development program (in addition to your pooled Phase 3 trials) to address the need for an evaluation of dermal safety,
- Outcome of any pregnancy or lactation exposures in your development program
- Available data regarding overdose, drug abuse, withdrawal and rebound of your drug product or the moiety
- Post marketing information regarding the safety of the moiety.

Refer to the *Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy-Clinical Overview and Clinical Summary of Module 2/Module 5: Clinical Study Reports.*

Question 9:
Does the Agency agree that the proposed clinical data from published literature, along with the Sponsor-conducted studies establish an adequate bridge for safety to support a 505(b)(2) NDA?

FDA Response to Question 9:
It is unclear if you intend to rely on the Agency's finding of safety and/or effectiveness for the final OTC monograph for Topical Acne Drug Products (21 CFR 333 Subpart D) to provide clinical information necessarily for approval. If you intend to rely on this OTC monograph, clearly specify which clinical information you intend to rely on in the 505(b)(2) NDA application and establish that such reliance is scientifically appropriate.

If you intend to rely, in part, 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.

Meeting Discussion:
The sponsor indicated that they tend to support the safety of their product using the OTC monograph and literature. The FDA stated that this plan appears reasonable.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 2:
Does the Agency agree that the action on the NDA for E-BPO Cream will meet the assessment is required?

FDA Response to Question 2:
Based on the information you have provided, your request for categorical exclusion as per 21 CFR 25.31(a) appears reasonable. However, the final determination will be made during the review of your NDA.

2.3. Nonclinical

Question 7:
Does the Agency agree that the proposed nonclinical data from published literature along with the nonclinical data package establish an adequate bridge for safety and are adequate to support a 505(b)(2) NDA?

FDA Response to Question 7:
We agree that the proposed nonclinical data from published literature and the nonclinical data package available for your topical drug product are adequate to support submission of a 505(b)(2) NDA application. Clearly specify which published literature provides pivotal nonclinical information in the NDA submission. Provide complete published literature reports used for pivotal nonclinical information in the 505(b)(2) NDA application. It is unclear if you intend to rely on the Agency's finding of safety and/or effectiveness for the final OTC monograph for Topical Acne Drug Products (21 CFR 333 Subpart D) to provide nonclinical information necessarily for approval. If you intend to rely on this OTC monograph, clearly specify which nonclinical information you intend to rely on in the 505(b)(2) NDA application and establish that such reliance is scientifically appropriate.

Meeting Discussion:
We acknowledge the newly submitted table and indicated if any additional information is needed, it will be communicated in post meeting communication.

2.4. Clinical Pharmacology

Question 21:
Does the Agency agree that based on Sol Gel's rationale, it is appropriate to request a waiver from conducting a thorough QT/QTc study?

FDA Response to Question 21:
We agree. Your rationale to request a waiver from conducting a thorough QT/QTc study appears acceptable.

In general, a waiver of assessments of QT interval prolongation is based on systemic exposure data and safety information. In your waiver request, provide a summary of the available data regarding the systemic exposure of your product after topical application and the results of your database searches for safety information regarding QT interval prolongation with the moiety (e.g. Drug Safety Information for Patients and Providers, the QT Drugs Database and PubMed.)

2.5. Clinical/Biostatistics

Question 3:
Does the Agency agree that the data from the Phase 3 studies support the proposed indication of "treatment of inflammatory lesions of rosacea"?

FDA Response to Question 3:
Based on the study designs and endpoints, your development program appears to support the proposed indication. However, labeling is data driven. It is premature to provide agreements regarding the labeling of your drug product. The content of labeling will be determined during the review of your New Drug Application (NDA).

Question 4:
Does the Agency agree that since the data from the Phase 3 studies support the conclusion that E-BPO Cream is effective (b) (4), the (b) (4) results can be included as a secondary endpoint?

FDA Response to Question 4:
See FDA Response to Question 3. However, your protocols did not prespecify efficacy endpoints (b) (4). In general, only endpoints that are pre-specified, clinically meaningful, and adjusted for multiplicity are eligible for consideration for labeling.

Question 5:
Does the Agency agree that E-BPO Cream is safe and efficacious for elderly patients 65 years of age and older?

FDA Response to Question 5:
See FDA Response to Question 3.

To support your conclusions regarding the safety of your drug product in subjects age 65 years and older and 75 years and older, provide a discussion of the safety findings [adverse events (AEs), adverse reactions (ARs) and abnormal safety parameters] from your pooled Phase 3 trials (and across your development program) in these populations compared with subjects age 18 to 65 years.

Question 6:
Does the Agency agree with the proposed adverse reactions (skin burning sensation and skin irritation) to be included in the labeling?

FDA Response to Question 6:
See FDA Response to Question 3.

Question 8:
Does the Agency agree that based on the results of the UV-visible absorption spectrum evaluation of E-BPO Cream and benzoyl peroxide raw material, no phototoxicity is anticipated in humans and a clinical photosafety evaluation is not required?

FDA Response to Question 8:
Yes, we agree.

In your meeting package, you submitted Study Report No. 2019-006 entitled “E-BPO cream, 5% UV/VIS Spectrum by Spectrophotometric Method – Photosafety evaluation”. As previously communicated (EOP2 Meeting Minutes dated 2/27/2018), if your topical drug product has no absorption in the UVB, UVA, or visible light spectrum you may submit a waiver for photosafety studies with your rationale and discussion.

Question 10:
Does the Agency agree that only the complete study reports and datasets from the IND studies are needed to support the planned 505(b)(2) NDA?

FDA Response to Question 10:
The application needs to be substantially complete at the time of submission. All literature that is necessary to support approval of your drug needs to be provided in the submission. In addition, provide a summary of the safety information from your non-IND trials in healthy volunteers and subjects with acne vulgaris.

Refer to the FDA Response to Question 9 and Administrative Comments regarding the 505(b)(2) regulatory pathway.

Question 11:
Does the Agency agree that, in principal, the proposed clinical program is sufficient to support the planned 505(b)(2) NDA and that no additional clinical studies are needed?

FDA Response to Question 11:
You propose to submit final study reports and datasets for the following trials in the 505(b)(2) NDA:

- Phase 2 Trial SGT-EBPO1-09: a multi-center, randomized, double-blind, vehicle-controlled, 12-week, dose-ranging study in subjects with mild, moderate or severe facial rosacea

- Phase 3 Trials SGT-54-01 and SGT-54-02: multi-center, double-blind, randomized, vehicle-controlled trials of S5G4T-1 in the treatment of papulopustular rosacea

- Phase 3 long-term safety Trial, SGT-54-07: a multi-center, open label, long-term safety study of S5G4T-1 to evaluate the safety of S5G4T-1 in subjects with papulopustular rosacea

In addition, you proposed to submit waivers for the assessment of thorough QT/QTc and photosafety. However, you also need to address the potential of your product to induce irritation and sensitization. If you propose to use assessments conducted during your Phase 3 trials (ratings of dryness, scaling, pruritis, stinging and burning) to support conclusions regarding the potential of your product to induce irritation and sensitization, include a discussion of how you distinguished signs and symptoms of the deterioration of the disease from the signs and symptoms of irritation and sensitization. Provide narratives for any subjects who were suspected of experiencing sensitization including a description of follow-up procedures (e.g. patch testing.)

Question 12:
Does the Agency agree that the proposed Study Data Standardization Plan (SDSP) is adequate to support the planned 505(b)(2) NDA?

FDA Response to Question 12:
From a technical standpoint the proposed SDSP is acceptable.

For the Phase 2 and Phase 3 studies, submit the SDTM and ADaM datasets in SAS transport format (.xpt). The analysis datasets should include all variables needed for conducting the analyses included in the study report.

Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Include statistical programs for the key primary and secondary analyses, including programs for the multiple imputation.

Question 13:
Does the Agency agree with the statistical analysis plan for the pooling of safety data for the Phase 3 clinical studies?

FDA Response to Question 13:
We agree with your plan to conduct your primary safety evaluation using pooled data from the two double-blind, vehicle-controlled Phase 3 Trials SGT-54-01 and SGT-54-02. You intend to conduct separate analyses of the safety data from Phase 2 Trial SGT-EBPO1-09 which evaluated a different formulation and dosage form of the proposed drug product and Trial SGT-54-07 which had a different study design and duration than the Phase 3 trials.

In order to compare the results from the Phase 2 trial with the pooled safety database, we recommend that you recode the adverse event data from the Phase 2 trial (MedDRA v 14.0) using the same MedDRA version as Phase 3 trials (MedDRA v 21.0).

Question 14:
Does the Agency agree with plan to provide the ISS text document in Module 2 and datasets in Module 5?

FDA Response to Question 14:
The integrated summary of safety (ISS) is a detailed integrated analysis of all relevant data from clinical study reports and is required by the regulations to be located in Module 5. If you believe Section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISS, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, a description of the contents of each section should be included in both Module 2 and Module 5 {21 CFR 314.50(d)(5)(v) and 21 CFR 377 314.50(d)(5)(vi)(a)}.

For additional information about the location of ISS and ISE in the CTD, refer to guidance for industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document at the FDA website.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

Additional Comments

1. For your Phase 2 and Phase 3 trials, provide subject narratives and Case Report Forms (CRFs) for all deaths, serious adverse events (SAEs), adverse events resulting in discontinuation of treatment, all pregnancies, and subjects who experienced hypersensitivity reactions. If the CRFs and narratives are located in the Clinical Study Reports (CSR), then provide links to this information in the relevant sections of the Overview of Clinical Safety and Summary of Clinical Safety.

2. Per 21 CFR 314.50, submit a 120-day, safety update report (SUR) to update the New Drug Application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. SUR must include the same kinds of summary information in the same format as the original submission. Ensure that you provide narratives and CRFs in the SUR for all subjects who died, experienced SAEs, hypersensitivity reactions, pregnancy, and discontinued the trial due to an AE. If the drug product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120-day safety update.

3. Provide the following in your analyses of the pooled safety data:
    - Summary Table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term reported by ≥1% of subjects.
    - Summary Table of Treatment-Emergent Treatment- Related Adverse Events (Adverse Reactions) by System Organ Class and Preferred Term reported by ≥1% of subjects.
    - Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.).
    - Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.
    - Shift tables for all vital signs. Provide the normal values for all parameters used in your analyses.
    - Shift tables for local safety assessments.
    - Safety analyses in subgroups of subjects by sex, race, age group (≥ 18 to < 65 years; ≥ 65 years; ≥ 75 years), ethnicity and baseline severity.
    - Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug.

4. At the time of NDA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The “coding dictionary” consists of a list of sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim) all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be

5. In your benefit-risk assessment for your drug product, we recommend that you provide the following information:

   A. Analysis of the condition which includes
      - Clinical manifestations (frequency and severity) and potential for progression
      - Prevalence in the general population and subpopulations
      - Proportion of patients who experience mild, moderate or severe disease
      - Severity across subpopulations (e.g. pediatric subgroups versus adult subgroups)
      - Impact on daily living in all populations and subpopulations
      - Uncertainties in the understanding of the condition
      - Subpopulations of special concern

   B. Current treatment options
      - Standard of care: list of approved therapies, drugs used off-label, nonprescription drugs, medical and surgical procedures, and non-drug therapies
      - Efficacy information and safety / tolerability issues associated with each these therapies
      - Uncertainties in the understanding of the risks and benefits of the treatment options
      - Adequacy of current therapies to meet the medical needs of the affected population and subpopulations (e.g. patients with refractory disease etc)

   C. Benefit
      - Trial design(s) and effect size
      - Limitations of the data
      - Clinical relevance of endpoints
      - Durability of benefit
      - Variation of benefit across subpopulations
      - Any exclusions in the studied population that would limit use in the general population
      - The number needed to treat (NNT) to achieve the treatment response/prevent bad outcome (e.g. likelihood of benefit)
      - Uncertainties in the evidence or about the drug product

   D. Risk
      - Ability of the safety database to reflect expected use in the patient population
      - The most important safety concern
      - Important aspects of the safety concern (e.g. range of severity, dose relationship,
      - prevention/mitigation, reversibility etc.)
      - Risks associated with suboptimal management of the disease
      - Uncertainties regarding risk

Question 15:
Does the Agency agree with the statistical analysis plan for the pooling of efficacy data for the Phase 3 clinical studies?

FDA Response to Question 15:
Your proposal to combine data from the Phase 3 Trials SGT-54-01 and SGT-54-02 into a pooled dataset to support the ISE analyses is acceptable.

Question 16:
Does the Agency agree with plan to provide the ISE text document in Module 2 and datasets in Module 5?

FDA Response to Question 16:
The integrated summary of efficacy (ISE) is a detailed integrated analysis of all relevant data from clinical study reports and is required by the regulations to be located in Module 5. If you believe Section 2.7.3 (Summary of Clinical Efficacy) would be sufficiently detailed to serve as the summary portion of the ISE, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. See also the FDA Response to Question 14.

Question 17:
Does the Agency agree that a graph showing the efficacy over time can be included in the label and the results (b) (4) can be included in this graph as an addition to the pre-specified results at Weeks 4, 8 and 12?

FDA Response to Question 17:
See FDA Response to Questions 3 and 4.

Question 18:
Does the Agency agree with the eCTD location of the BIMO data that will be included in the 505(b)(2) NDA?

FDA Response to Question 18:
Your proposed eCTD location in Section 5.3.5.4 is acceptable.

Question 19:
Does the Agency agree (b) (4)
(b) (4)

FDA Response to Question 19:
Comments are pending internal consultation.

Question 20:
Does the Agency agree the [redacted] (b) (4) can be included as part of the product labeling?

FDA Response to Question 20:
See FDA Response to Question 3.

[redacted] (b) (4)

In general, inclusion of PRO data in the drug labeling will depend on, but is not limited to the following:

- Relevance and importance of the concept(s) of interest to the target patient population
- Strengths and limitations of the instrument within the given context of use
- Design and conduct of the trial
- Adequacy of submitted data (e.g., rigorous data collection, methods to handle missing data, etc.)
- Magnitude of the statistically significant and clinically meaningful treatment effect

Additional comments are pending internal consultation.

3.0 ADMINISTRATIVE 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*.[1] 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 FDA.gov.[2]

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 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)).

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[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

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

MANUFACTURING FACILITIES

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA

investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

4.0 ATTACHMENTS AND HANDOUTS

Sponsor's Agenda

- Discuss responses to Question 9, Question 7 and Questions 19/20 together. Attached is one hand out that we are providing to support discussion of Question 7; this is a table included in the Briefing Package that outlines the nonclinical publications (see attached handout)

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

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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/

KENDALL A MARCUS
02/21/2020 04:36:20 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102233

MEETING MINUTES

Sol Gel Technologies, Ltd.
c/o B&H Consulting Services, Inc.
Attention: Elizabeth N. Dupras, RAC
Director, CMC and Global Regulatory Affairs
50 Division Street, Suite 206
Somerville, NJ 08876

Dear Ms. Dupras:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for benzoyl peroxide cream, 5%.

We also refer to the meeting between representatives of your firm and the FDA on November 29, 2017. The purpose of the meeting was to obtain Agency agreement to the general CMC and clinical strategies to support the safety and efficacy of benzoyl peroxide cream in the Phase 3 study and the 505(b)(2) NDA.

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

If you have any questions, call Barbara Gould, Chief, Project Management Staff at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	November 29, 2017 @ 10:00 a.m.
Meeting Location:	White Oak Campus Silver Spring, Maryland
Application Number:	IND 102233
Product Name:	benzoyl peroxide cream, 5%
Proposed Indication:	for the topical treatment of inflammatory papules and pustules of rosacea
Sponsor:	Sol-Gel Technologies
Meeting Chair:	Kendall Marcus
Meeting Recorder:	Barbara Gould

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Dennis Bashaw, PharmD, Director, Division of Clinical Pharmacology (DPC) III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, DPC III
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP III
Yichun Sun, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Elektra Papadopoulos, MD, Director, Clinical Outcomes Assessments
Vidual Kolhotkar, PhD, Acting Biopharmaceutics Team Lead, Division of Biopharmaceutics, Office of New Drug Producs (DB/ONDP)
Bryan Ericksen, PhD, Biopharmaceutics Reviewer, DB/ONDP
Bryan S. Riley, PhD, Acting Branch Chief, Division of Microbiology Assessment Branch II, Office of Product Quality
Denise Miller, Sr. Microbiology Reviewer, DMA/Branch II
John McMichael, Biomedical Engineer, CDRH
Steven Basile, Biomedical Engineer, CDRH
Rong Guo, Biologist, CDRH

Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES
Ofra Levy Hacham, Ph.D., Vice President Quality and Regulatory Affairs, Sol Gel Technologies Ltd.
Ofer Toledano, Ph.D., Vice President Research & Development, Sol Gel Technologies Ltd.
Miri Nadler Milbauer, Ph.D., MBA, Regulatory Affairs Manager, Sol Gel Technologies Ltd.
(b) (4)
Stephanie M. Pierson, RAC; President, B&H Consulting Services, Inc. (Regulatory Consultant)
Elizabeth N. Dupras, RAC, Director, CMC and Global Regulatory Affairs, B&H Consulting Services, Inc. (US Agent and Regulatory Consultant)

1.0 BACKGROUND

Purpose
To obtain Agency agreement to the general CMC and clinical strategies to support the safety and efficacy of benzoyl peroxide cream in the Phase 3 study and the 505(b)(2) NDA

2.0 BACKGROUND

Purpose
To obtain Agency agreement to the general CMC and clinical strategies to support the safety and efficacy of benzoyl peroxide cream in the Phase 3 study and the 505(b)(2) NDA

Regulatory History

We have sent the following correspondences:
- May 1, 2012 Advice/Information Request
- April 22, 2010 Advice/Information Request
- October 21, 2009 Advice/Information Request

3.0 DISCUSSION

Introductory Comments

You are developing a novel formulation of benzoyl peroxide [Encapsulated Benzoyl Peroxide (E-BPO) cream] for the topical treatment of inflammatory lesions (papules and pustules) of rosacea. To date, you have conducted the following trials:

1. **Non- IND** Trials (healthy volunteers and subjects with acne vulgaris)

- **KGL 5316:** An open-label, single center trial to investigate the effect of 3% E-BPO cream on *P. acnes* after twice daily application to the forehead for 4 weeks in 15 healthy subjects.
- **KGL 5651**: A randomized bilateral comparison of the effects of two formulations of 3% E-BPO (dosage forms/ formulations not specified) on *P. acnes* on the cheeks of 16 healthy subjects after 4 weeks of twice daily applications.
- **KGL 5782:** A randomized bilateral comparison of the effects of 2.5% E-BPO (dosage form/ formulation not specified) and 2.5% Proactiv on *P. acne* on the cheeks of 16 healthy subjects after 4 weeks of twice daily applications.
- **KGL 6033**: A randomized bilateral comparison of the effects of two formulations of 4% E-BPO (dosage forms/ formulations not specified) on *P. acnes* on the cheeks of 16 healthy subjects after 4 weeks of twice daily applications.
- **SGT-03A**: A randomized, 4 week, double blind trial, to evaluate the efficacy, safety and tolerability of 10% Cool-Pearls™ BPO (dosage form/ formulation not specified) compared with Clearasil®10% BPO applied twice daily in 35 subjects with mild to moderate acne.
- **SGT-03B**: A randomized, 4 week, double blind, Phase 2 trial, to evaluate the efficacy, safety and tolerability of 7% and 10% of Cool Pearls™ BPO (dosage form/ formulation not specified) compared with Proactiv 7% applied twice daily in 73 subjects with mild to moderate acne.
- **SGT-04:** A randomized, 4 week, double- blind, Phase 3 trial, to compare the efficacy, safety and tolerability of Regular (4%) and Extra Strength (7%) Cool Pearls™ BPO kits (dosage form/ formulation not specified) with Proactiv® Regular (2.5%) and Extra (7%) Strength BPO kits applied twice daily in 78 subjects with mild to moderate acne.

You conducted these trials in different study populations and used different formulations/ concentrations/ dosage forms than the proposed E-BPO cream.

2. **IND Trial** (subjects with mild, moderate or severe facial rosacea)

   You completed Phase 2 **Trial SGT-EBPO1-09**, a multi-center, randomized, double-blind, vehicle-controlled, 12 week, dose-ranging trial. Eligible subjects had mild, moderate or severe facial rosacea based on the Investigator Global Assessment Scale (IGA) and at least 12 inflammatory papules or pustules. A total of 92 subjects who met the inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to 5% E-BPO Gel, 1% E- BPO Gel, or Vehicle Gel. Subjects applied the study product once daily for 12 weeks. Assessments of IGA, inflammatory lesion counts, erythema, telangiectasia and local safety (dryness, scaling, pruritus, stinging and burning) were conducted at Screening, Baseline, and Weeks 4, 8, and 12.

   The primary efficacy endpoints were:
   - Proportion of subjects with the primary measure of success, defined as a 2-grade improvement in the IGA relative to Baseline at Week 12, with the Week 12 IGA of clear or almost clear.

- Change in inflammatory lesion count at Week 12.

Results

Efficacy
Primary efficacy endpoints at Week 12

- The proportions of subjects with the primary measure of success: 20.0% (6/30) for Vehicle Gel, 37.5% (12/32) for 1% E-BPO Gel, and 53.3% (16/30) for 5% E-BPO Gel.
- The least squares (LS) mean changes from Baseline in inflammatory lesion counts at Week 12 were -8.8 (95% CI: -15.1, -2.5) for Vehicle Gel, -21.5 (95% CI: -27.5, -15.4) for 1% E-BPO Gel, and -14.7 (95% CI: -21.0, -8.4) for 5% E-BPO Gel.

Safety

- No deaths or SAEs were reported during the study.
- There were severe local reactions in 3 subjects resulting in withdrawal from the trial in 2 subjects.

This trial was conducted with a drug product (5% E-BPO Gel, 1% E- BPO Gel) that is different (formulation/ dosage form) than the proposed drug product (5% E-BPO Cream) for the Phase 3 clinical trials. Therefore, the safety and efficacy data from Trial SGT-EBPO1-09 may have limited utility unless the sameness of the formulations before and after the changes can be demonstrated by in vitro and in vivo studies. (See Response to Question 5.)

2.1. General Regulatory

Question 1:
Does the Agency agree that a 505(b)(2) NDA is appropriate?

FDA Response to Question 1:
If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you and for which you have not obtained a right of reference (e.g., FDA's finding of safety and/or effectiveness for a listed drug(s), published literature, OTC monograph), then your marketing application will be a 505(b)(2) application. 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. You also must establish that reliance on studies described in the literature or on other studies is scientifically appropriate.

You state that benzoyl peroxide is included as the active ingredient in multiple prescription and OTC monograph products. Clarify which source(s) of information (e.g., listed drug(s), OTC monograph, published literature) you propose to rely upon for approval of your NDA, what information and sections of your NDA (e.g., nonclinical, clinical), including the labeling, you intend to support through such reliance, and how you will establish the bridge

between your proposed drug product and each source of information upon which you propose to rely.

Refer to the **505(b)(2) Regulatory Pathway** section below for additional information about submitting a 505(b)(2) NDA.

2.2. Chemistry, Manufacturing, and Controls

Question 2:
Does the Agency agree that the proposed information is adequate to support the use of these noncompendial excipients [redacted] (b) (4) in the Phase 3 clinical supplies and the 505(b)(2) NDA?

FDA Response to Question 2:
The information proposed for the noncompendial excipients, cetrimonium chloride and polyquaternium-7, is not deemed adequate. We have the following recommendations for you to modify the specification of cetrimonium chloride:

- Add two identification tests for cetrimonium chloride.
- Add a test with an acceptance criterion [redacted] (b) (4).
- Using stability indicating methods (i.e. HPLC methods) for assay and impurity tests.

We have the following recommendations for you to modify the specification of polyquaternium-7:

- Add two identification tests for polyquaternium-7.
- Add an assay test with an acceptance criterion for polyquaternium-7 using a stability indicating method (i.e. HPLC method).
- Add a test with an acceptance criterion [redacted] (b) (4) [redacted] (b) (4).
- Add a test for the molecular weight of polyquaternium-7.

Question 3:
Does the Agency agree with Sol-Gel's characterization of the active ingredient in E-BPO Cream as microencapsulated benzoyl peroxide?

FDA Response to Question 3:
The characterization studies performed on microencapsulated benzoyl peroxide appear reasonable. However, we have the following recommended tests to be included in the specification of microencapsulated benzoyl peroxide:

- Test of the specific surface area of the [redacted] (b) (4) benzoyl peroxide microcapsules.
- Test of the [redacted] (b) (4) benzoyl peroxide microcapsules.
- Zeta potential of the [redacted] (b) (4)% E-BPO suspension.

- Ionic strength of the medium of the (b) (4)% E-BPO suspension.

Question 4:
Does the Agency agree that the IVRT data and the proposed acceptance criteria (release and stability) for the E-BPO Cream drug release test are adequate to demonstrate that E-BPO Cream is an (b) (4) formulation?

FDA Response to Question 4:
To date, (b) (4) terminology has only been used for oral/parenteral products. The claim has to be substantiated with appropriate in-vivo data as per the requirements outlined in 21 CFR 320.25 (f). It is unclear how the claimed (b) (4) properties can be demonstrated in vivo because your product is a locally acting topical product and, due to its rapid conversion to benzoic acid, an in vivo bioavailability assessment appears to be not feasible. The claim, (b) (4), itself is not possible as an in vitro demonstration would not be acceptable: you cannot expect an in vitro model to replicate diseased skin conditions, nor have you provided any clinically meaningful explanation as to how (b) (4) a topical product could be accomplished.

Regarding the IVRT method acceptance criteria, drug release rate and not % release is an appropriate approach for semi-solids. Report data in units of $mcg/cm^2/hr^{1/2}$.

Question 5:
Does the Agency agree that the proposed specification is adequate to support the safety and quality of E-BPO Cream in the planned Phase 3 study and the 505(b)(2) NDA?

FDA Response to Question 5:
In addition to the tests listed in the drug product specification, we recommend you add a test for globule size of the dispersed phase of the cream. Additional tests may also be requested to be included in the drug product specification for the delivery pump of the drug product by the Center for Devices and Radiological Health (CDRH) if the pump is deemed to be a device.

Question 6:
Does the Agency agree that the changes in the formulation and manufacturing process do not impact the quality of the drug product?

FDA Response to Question 6:
We do not agree that the changes in the formulation and manufacturing process do not impact the quality of the drug product unless the sameness of the formulations before and after the changes can be demonstrated by in vitro and in vivo studies.

Additional Comments
We have the following comments for the eventual NDA submission:

1. A demonstration of the effectiveness (b) (4) (b) (4)

[redacted] should be included in the final NDA submission. This can be a one-time development study [redacted]

2. You have provided limited information about the pump that you intend to market, the Agency expects that your future NDA submission will contain detailed design and functionality information to demonstrate how the device achieves your intended use. You will need to ensure the pump you intend to market meets the user requirements for delivery of the drug (e.g. force to actuate pump, delivered dose uniformity). Additionally, you will need to ensure the device performs as specified for its intended lifetime of use. Safety related specifications, such as device biocompatibility and microbial control of the container closure system and the final product, should also be addressed.

2.3. Nonclinical

Question 7:
Does the Agency agree that no further nonclinical studies are needed to support the 505(b)(2) NDA?

FDA Response to Question 7:
Your proposal appears reasonable but you need to specify what source(s) of information you propose to rely upon for approval of your NDA and how you will establish the bridge between your proposed product and each source of information upon which you propose to rely. See FDA Response to Question 1.

2.4. Clinical/Biostatics/Clinical Outcome Assessment

Question 8:
Does the Agency agree that the 5% dosage strength for E-BPO Cream is appropriate for the planned Phase 3 study?

FDA Response to Question 8:
The proposed 5% E- BPO Cream may be appropriate for the planned Phase 3 trials. However, the Phase 2 trial was conducted with the different study product (formulation /dosage form) than the proposed study product intended for the Phase 3 clinical trials. In addition, the IGA scale that was used in your Phase 2 trial is not adequate. The category of "Clear" does not represent the true absence of disease (mild erythema). The severity of

erythema was graded as "no", "very mild", "mild", "moderate" and "severe". The levels of disease severity were not defined by using morphologic descriptors that describe that specific level of disease severity (slightly pink erythema to dark red erythema). The categories of "Clear" and "Almost clear" are not distinct. In addition, nodules may be observed in phymatous and granulomatous rosacea but are not a characteristic feature of papulopustular rosacea. We recommend that you remove the descriptors that relate to nodules from your scale.

The scale was not included in your briefing package but is provided below (SD 13, Clinical Study Report SGT-EBPO1-09, page 26).

Investigator Global Assessment Scale (IGA)

Score	Severity Grade	Description
0	Clear	No inflammatory lesions present, No or very mild erythema immediately localized to and around where inflammatory lesions were present.
1	Almost clear	Very mild erythema immediately localized to and around inflammatory lesions, Very few small papules/pustules.
2	Mild	Mild erythema immediately localized to and around inflammatory lesions, A few small papules/pustules.
3	Moderate	Moderate erythema immediately localized to and around inflammatory lesions, Several small or large papules/pustules, Up to two nodules.
4	Severe	Severe erythema immediately localized to and around inflammatory lesions, Numerous small and or large papules/pustules, May be several nodules

Question 9:
Does the Agency agree with the proposed Phase 3 study design?

FDA Response to Question 9:

You proposed to conduct two identical, multi-center, double-blind, randomized, vehicle controlled, Phase 3 trials to evaluate the efficacy and safety of E-BPO Cream or the topical treatment of inflammatory lesion of rosacea (papules and pustules). You intend to enroll 350 male and female subjects in each trial who are at least 18 years of age with moderate to severe papulopustular rosacea (Grade 3 or 4 on the IGA). Subjects will be randomized in a 2:1 ratio to receive the proposed product or vehicle applied in a thin layer once daily to the affected areas of the face for 12 weeks. Investigational staff will conduct assessments at screening, baseline, Weeks 2, 4, 8, and 12. Both study products will be supplied in (b) (4)-gram pumps.

At each visit, the following efficacy assessments will be performed: inflammatory (papules, pustules) lesion counts, 5-point Investigator Global Assessment (IGA) scale, and evaluation of "inflammatory lesion erythema", "rosacea erythema", and telangiectasia. Safety monitoring will include local adverse events, monthly pregnancy testing, the Investigator Cutaneous Safety Assessment rating of erythema and scaling on a 4-point scale ranging from 0 (None) to 3 (Severe), and Patient Reported Outcomes (PRO) measures.

Primary efficacy endpoints

- Proportion of subjects with the primary measure of success, clear (0) or almost clear (1) in the IGA at Week 12.
- Change in inflammatory lesion count at Week 12.

Secondary efficacy endpoints

- (b) (4)
- Percent change in inflammatory lesion count at Week 12
- Proportion of subjects with a measure of success, defined as a 2-grade improvement in the IGA relative to Baseline at Week 12
- (b) (4)

In general, your proposed design for two Phase 3 trials appear reasonable; however, you have not provided any rationale for your proposed sample size. We have the following comments on your brief synopsis as you draft complete protocols.

- You have proposed several secondary endpoints. Secondary endpoints should be clinically meaningful, limited in number, supportive of the primary endpoints, and adjusted for multiplicity to be considered for labeling.

- You have stated that the change in inflammatory lesions endpoint will be analyzed with an ANCOVA analysis on either the original data or ranked data. The protocol should specify clear guidelines for selecting the primary analysis method to ensure that the statistical methods are adequately prespecified to avoid introducing bias.

- You have proposed handling missing data using Markov Chain Monte Carlo multiple imputation. Your protocols should include full details of the proposed multiple imputation procedure including such information as the imputation and analysis models, any necessary transformations, the number of imputations, and randomization seeds, etc. In addition to the primary method of handling missing data, you should propose at least two sensitivity analyses that use alternate assumptions to ensure that the method of handling missing data does not impact the results.

  Clarify whether you intend to manage age group enrollment via stratification and whether your target of 6% of subjects age 65 years and older is consistent with the age distribution of your target population. If you intend to use stratified randomization, then we recommend including the stratification factors in your analysis models.

- For the proposed indication, the recommended co-primary endpoints are

    - success on an adequate IGA scale defined as the proportion of subjects achieving "Clear" (0) or "Almost clear" (1) at Week 12, AND

    - absolute change in inflammatory lesion counts from baseline to Week 12.

- You did not include your 5-point IGA scale in your protocol synopsis. The IGA scale should be static, noncomparative with a limited number of categories. Each category should be distinct and non-overlapping and should represent a clinically meaningful gradation of disease. The category of "Clear" should represent the true absence of disease (no erythema). Each level of disease severity should be defined by using morphologic descriptors that describe that specific level of disease severity. See response to Question 8.
- In general, your proposed safety evaluation which includes a cutaneous safety assessment (Investigator Cutaneous Safety Assessment score), urine pregnancy testing (UPT) in females of child-bearing potential (FCBP) and adverse events (AEs) is acceptable. However, because you did not include your Investigator Cutaneous Safety Assessment scale, it is difficult to evaluate the adequacy of the local safety evaluation. In addition, consider adding a physical examination at Week 12, a follow-up assessment for safety after the end of treatment and a periodic vital sign assessment.
- (b) (4)

- We recommend that during the trial that investigators remind subjects to avoid exposure to sunlight and sunlamps and to wear sunscreen when sun exposure cannot be avoided.

Question 10:
Does the Agency agree that the planned enrollment of approximately 6% of the study population in the 65 years and older age group is adequate to demonstrate the safety and effectiveness of E-BPO Cream in geriatric rosacea patients?

FDA Response to Question 10:
Provide epidemiologic data to support your proposal to limit the size of the study population age 65 years and older to 6%.

Question 11:
Does the Agency agree that long-term safety studies are not needed for E-BPO Cream?

FDA Response to Question 11:

No, we do not agree. Given the chronic nature of the proposed indication, you should address the long-term safety of your drug product for the proposed indication in the target population. Results of long-term safety assessments in subjects with acne may be substantially different than of long term safety assessments in subjects with rosacea whose aging skin is thinner, more fragile and sensitive.

You may find relevant information in the ICH guideline for industry E1a– The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions.

Question 12:
Does the Agency agree that (b) (4) (b) (4)

FDA Response to Question 12:
Patient Assessment of Papulopustular rosacea Signs and Symptoms (PAPSS)
We agree that the data accumulated thus far (literature review, expert input, patient input) support the content validity of the PAPSS as a measure of patient-reported signs and symptoms of papulopustular rosacea.

However, we do not agree that (b) (4) (b) (4)

Patient Assessment of Papulopustular Rosacea Impacts (PAPI) and PGIS
Your briefing package states that (b) (4) PAPI and PGIS will provide supportive efficacy data. It appears that the PAPI and PGIS will be used to support exploratory endpoints. At this time, we have insufficient information to comment fully on these two instruments in the absence of supportive evidence and your intended use for these instruments (b) (4) (b) (4). You would need to provide details (b) (4) (b) (4) and general plans for analysis for us to provide a more concrete recommendation.

Additional comments:
We recommend you explore multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the PAPSS from the patient perspective. (b) (4) (b) (4)

(b) (4)

Question 13:
Does the Agency agree that the toxicology data are adequate to demonstrate the photosafety of E-BPO Cream?

FDA Response to Question 13:
We recommend that you provide the UV-visible absorption spectrum for your product. If any of the components of the drug product absorb light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible) then you need to conduct a clinical photosafety evaluation.

Refer to S10 Photosafety Evaluation of Pharmaceuticals Guidance for Industry http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Question 14:
Does the Agency agree that it is reasonable to request a waiver from conducting pediatric studies for E-BPO Cream?

FDA Response to Question 14:
Your proposal to request a waiver from conducting pediatric studies for E-BPO Cream may be reasonable. However, you will need to submit a Pediatric Study Plan (PSP) for review within 60 days of the End- of- Phase (EOP2) meeting with your request for a deferral, partial waiver or waiver, along with your rationale and supporting information. Refer to Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry (March 2016) http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Refer to the Administrative Comments at the end of this document.

Question 15:
Does the Agency agree that the clinical development plan is adequate to support a 505(b)(2) NDA, and that no additional clinical studies are needed?

FDA Response to Question 15:
Your proposed clinical development program for E-PBO Cream includes the trials tabulated below:

Study Category	Study Type	Planned Number of Subjects
Phase 1	Human Repeat Insult Patch Test (Skin Irritation Potential)	40
	21-day Cumulative Irritation Test (Sensitizing Potential)	240
Phase 2	Double-Blind, Randomized, Vehicle-Controlled, Dose-Range Study of Encapsulated Benzoyl Peroxide Gel, 1% and 5%, and Vehicle Gel in the Treatment of Rosacea	92 (30 each in the 5% and vehicle arm; 32 in the 1% arm) (COMPLETED)
Phase 3 (two replicate studies)	Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of E-BPO Cream, 5% in the Treatment of Papulopustular Rosacea	702 (468 in active arm and 234 in vehicle arm)

We have the following comments regarding the overall clinical program:

- You propose to conduct provocative studies (cumulative irritation and sensitization) to evaluate the dermal safety of your drug product prior to marketing; however, these studies are not required. As discussed in the response to Question 13, you will need to submit a UV-visible absorption spectrum for your product and address photosafety.

- As the treatment of rosacea would be considered a chronic indication, (i.e., the drug may be used for a period of 6 months or greater), you need to address long term safety as discussed in the response to Question 11.

- You will need to address the cardiovascular safety of your product in accordance with the guidance for industry: *E14 Clinical Evaluation of QT/QTc Interval prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* It may be reasonable to submit a waiver which includes your rationale.

Post-meeting Comments:

(b) (4)

(b) (4)

3.0 Administrative 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. Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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

c. Number of subjects treated who prematurely discontinued for each site by site

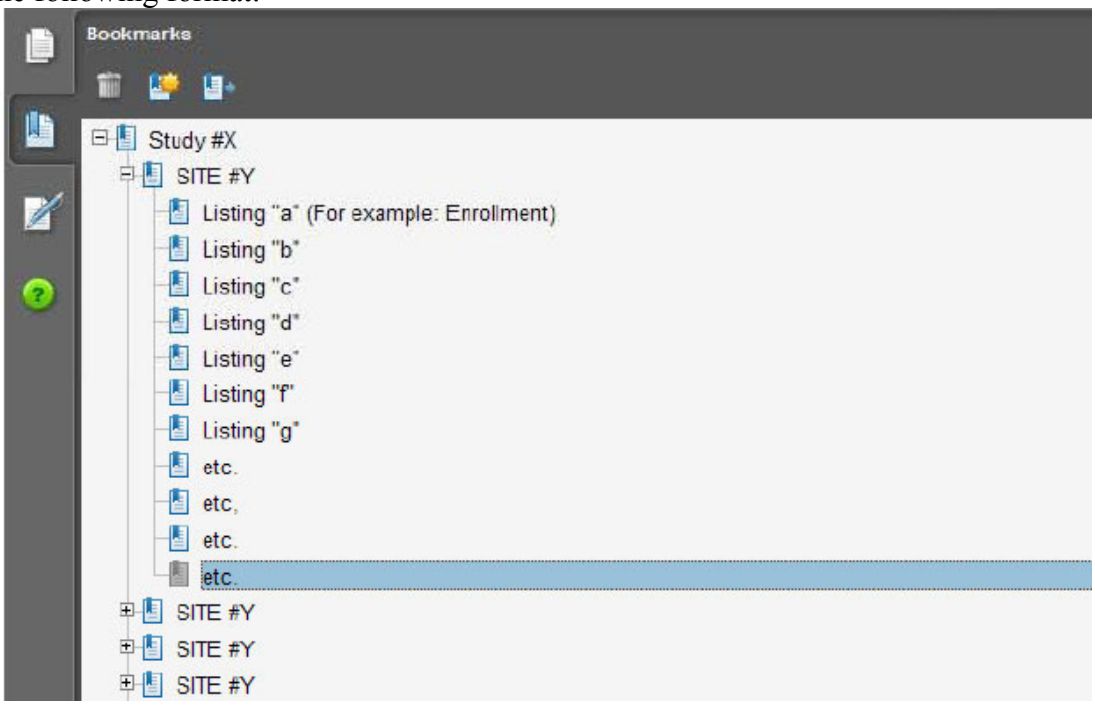
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ATTACHMENTS AND HANDOUTS

Upon receipt of FDA preliminary meeting comments, the sponsor requested to focus the meeting on the following questions:

- Question 8
- Questions 9 to 11
- Question 12
- Questions 2 to 5

Sol-Gel acknowledges the responses to all other questions, and these recommendations will be considered as development continues.

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

/s/

KENDALL A MARCUS
02/27/2018