CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214902Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125961

MEETING MINUTES

Sol-Gel Technologies, Ltd.
c/o B & H Consulting, 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 and tretinoin cream, 3%/0.1%.

We also refer to the telecon between representatives of your firm and the FDA on March 16, 2020. The purpose of the meeting was to discuss format and content for submission of proposed 505(b)(2) NDA.

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 Dentistry
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Agenda

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 16, 2020 @ 1:00 P.M.
Meeting Location: White Oak, Building 22 Conference Room 1315

Application Number: IND 125961
Product Name: benzoyl peroxide and tretinoin cream, 3%/0.1%

Proposed Indication: For the topical treatment of acne vulgaris (acne) in patients nine years of age and older
Sponsor Name: Sol-Technologies, Ltd

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

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Roselyn E. Epps, MD, Clinical Reviewer, DDD
Barbara Hill, PhD, Pharmacology Supervisor, DDD
Jill Merrill, PhD, Pharmacology Reviewer, DDD
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) 3
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDD
Craig Johnson, PharmD, Regulatory Health Project Manager, DDD
David Nartey, PharmD, Regulatory Health Project Manager, DDD
Kimberle P. Searcy, MPH, Regulatory Health Project Manager, DDD
Qianyiren Song, PharmD, Regulatory Health Project Manager, DDD

SPONSOR ATTENDEES

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.
(b) (4) Medical Consultant for Sol-Gel Technologies Ltd.
(b) (4) Statistical Consultant for Sol-Gel Technologies Ltd.

[redacted] (b) (4) CMC Consultant for 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 content and format for submission of proposed 505(b)(2) NDA.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 05/09/2018 End of Phase 2 Meeting
- 06/10/2015 PIND Meeting

We have sent the following correspondences:

- 05/01/2019 Pediatric Study Plan – Written Response
- 10/05/2018 Advice Letter
- 08/08/2018 Special Protocol – Agreement
- 04/12/2016 Advice Letter
- 03/02/2016 Study May Proceed Letter

2.0 DISCUSSION

2.1. Regulatory

Question 1:
Does the Agency agree with the organization of the eCTD NDA?
FDA Response to Question 1:
The Agency does not agree with the organization of the eCTD NDA regarding Modules 2.6.6, 2.7.1, 2.7.2, 2.7.3, 2.7.4, and 3.2.R. Additional nodes should not be created in the eCTD structure beyond what is in the specifications. Follow https://www.fda.gov/media/76444/download for more details regarding the eCTD structure specifications. Instead, leaf titles can be used to differentiate between documents. For further guidance on acceptable submission format per Module, follow https://www.fda.gov/media/71551/download.

While the Agency agrees with the submission of Module 3.2.S for each substance, note that in Module 2.3.S, one document should be submitted for each drug substance. Follow https://www.fda.gov/media/71551/download for more details.

From technical perspective (and not content related), the proposed organization of the other Modules is acceptable.

Question 2:
Does the Agency agree that the information provided from the OTC monograph and literature for benzoyl peroxide is sufficient to address the requirements to support a 505(b)(2) NDA?

FDA Response to Question 2:
We agree that the information provided from the OTC monograph and literature for benzoyl peroxide is sufficient to address the nonclinical requirements to support a 505(b)(2) NDA.

2.2. Chemistry, Manufacturing and Controls (CMC)

No CMC questions were submitted for this meeting. A separate PNDA meeting is scheduled with CMC.

2.3. Nonclinical

No nonclinical questions were submitted for this meeting.

2.4. Clinical Pharmacology

Question 3:
Does the Agency agree that the MUSE PK study data establish an adequate bridge to support clinical pharmacology and safety of tretinoin in E-BPO/E-ATRA Cream in a 505(b)(2) NDA?

FDA Response to Question 3:
The design of your completed maximal use study (MUsT) and relative bioavailability study appears reasonable. The adequacy of this study to support establishment of a clinical bridge with the listed drug will be reviewed at the time of your NDA submission. We recommend you submit relative bioavailability data by calculating the 90 percent confidence interval (CI) on the ratio of the geometric mean of Cmax and AUC between your product and the listed drug for review in your NDA submission.

Question 4:
Does the Agency agree that, based on the MUSE PK study data, no long-term safety study for E-BPO/E-ATRA Cream is required to support the 505(b)(2) NDA?

FDA Response to Question 4:
As previously communicated at the EOP 2 meeting on May 9, 2018, additional long-term systemic safety data may not be necessary if the systemic exposure of tretinoin

observed in your maximal use PK study does not exceed that observed for other marketed topical tretinoin products. This is a review issue under the NDA.

Question 5:
Does the Agency agree that based on the MUSE PK study data, a waiver can be requested for conducting a thorough QT/QTc study?

FDA Response to Question 5:
Your proposal to submit a waiver request for QT/QTc assessment appears reasonable. Final determination will be made at the time of NDA review.

2.5. Clinical/Biostatistics

Question 6:
Does the Agency agree that the clinical study reports and datasets from these IND studies are adequate to support the planned 505(b)(2) NDA and that no additional clinical studies are needed?

FDA Response to Question 6:
We agree that the listed clinical trial reports are adequate to support filing of your NDA. The adequacy of the clinical data to support your proposed indication will be a review issue under the NDA.

Question 7:
Does the Agency agree that the safety data provided in the Phase 1 study, SGT-65-06, confirm that the product is safe and has a negligible level of irritation?

FDA Response to Question 7 and 8:
Data from dermal safety studies SGT-65-06, SGT-65-08 and SGT-65-09, as well as the local safety from your other trials, will be reviewed and safety assessed with submission of your NDA.

Question 8:
Does the Agency agree that the safety data provided in the Phase 1 studies, SGT-65-08 and SGT-65-09, confirm that the product is safe for use when exposed to daylight?

FDA Response to Question 8:
See FDA Response for Questions 7 and 8. Appropriate labeling for Ultraviolet Light and Environmental Exposure information may be typical for tretinoin products.

Question 9:
Does the Agency agree that the proposed SDSP is adequate to support the planned 505(b)(2) NDA?

FDA Response to Question 9:
From a technical standpoint the proposed SDSP is acceptable.

Your proposal to submit SDTM and ADaM formatted datasets for the NDA submission is acceptable.

The primary method for handling the missing data is the Markov Chain Monte Carlo (MCMC) multiple imputation (MI). Sensitivity analyses for the handling of missing data include a model-based multiple imputation procedure and a tipping point analysis. Submit the SAS code used to implement the proposed multiple imputation methods as well as the SAS code used to analyze the imputed datasets. In addition, submit the SAS code to implement the tipping point analysis.
For the analysis datasets, we have the following general comments:

1. Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the Phase 3 trials.

2. The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 10:
Does the Agency agree with the statistical analysis plan for pooling of efficacy data of the two Phase 3 clinical studies?

FDA Response to Question 10:
Your proposal to pool efficacy data from the two identically-designed Phase 3 trials for the integrated summary of efficacy (ISE) is acceptable. We note that the objective of the integrated summary of efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooled data. Therefore, analyses based on pooled efficacy data are considered exploratory.

Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

Question 11:
Does the Agency agree with the plan to provide the ISE discussion in Module 2.7.3 and tables, listings and figures and datasets in Module 5.3.5.3?

FDA Response to Question 11:
From technical perspective (and not content related), the proposed ISE organization is acceptable.

This is acceptable as long as the size and content conform with the Agency guidance, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

Question 12:
Does the Agency agree with the statistical analysis plan for pooling of safety data of the two Phase 3 clinical studies.?

FDA Response to Question 12:
Your plan for pooling safety data appears reasonable provided that you pool from the two identically-designed Phase 3 trials.

Question 13:
Does the Agency agree with the plan to provide the ISS discussion in Module 2.7.4 and tables, listings and figures and datasets in Module 5.3.5.3?

FDA Response to Question 13:
From technical perspective (and not content related), the proposed ISS organization is acceptable.

This is acceptable as long as the size and content conform with the Agency guidance, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

Question 14:
Does the Agency agree that Items 1 (pimples) and 5 (embarrassment) of the PRE-FACE support the Phase 3 clinical studies primary endpoint and provide direct evidence of treatment benefit in terms of patient-reported improvement in the visual attributes and perceived emotional impacts of acne vulgaris in the target patient population?

FDA Response to Question 14:
We note that the endpoint of at least a 4-point reduction on Item 1 (pimples) of the PRE-FACE from baseline to Week 12 failed to show statistical significance in one of the two Phase 3 trials, while the endpoint of at least a 4-point reduction on Item 5

(embarrassment) of the PRE-FACE from baseline to Week 12 failed to show statistical significance in both Phase 3 trials. Replication of study findings for the endpoint based on PRE-FACE Item 1 was not achieved.

Question 15:
Does the Agency agree that the effect of treatment on patient reported acne signs (pimples, blackheads and whiteheads) and symptoms (redness) observed in the Sponsor's Phase 3 studies, as assessed by the PRE-FACE, reflect a meaningful therapeutic benefit to patients?

FDA Response to Question 15:
See above comments. Additional comments may be forthcoming as your submission is still under review by the COA team. (b) (4) (b) (4)

Question 16:
Does the FDA agree to the eCTD location of the BIMO information that will be included in the 505(b)(2) NDA?

FDA Response to Question 16:
From technical perspective (and not content related), the proposed BIMO organization is acceptable.

Meeting Discussion:
The sponsor inquired about the status of their Agreed iPSP submitted May 2019. The Agency noted that the Agreed iPSP was currently under review and a final determination is forthcoming.

3.0 ADMINISTRATIVE COMMENT

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]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

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[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] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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

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

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

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)				

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).[7] 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.[8]

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

[7] 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.
[8] http://www.regulations.gov

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 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*.[9]

4.0 ATTACHMENTS AND HANDOUTS

Sponsor's Agenda

- Question 4
- Question 15
- PREA Requirements

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

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
03/18/2020 07:36:05 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 125961

MEETING MINUTES

Sol-Gel Technologies, Ltd.
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 and tretinoin topical cream, 3%/0.1%.

We also refer to the meeting between representatives of your firm and the FDA on May 9, 2018. The purpose of the meeting was to discuss Phase 3 development program to support a 505(b)(2) NDA for benzoyl peroxide and tretinoin topical cream, 3%/0.1% for the treatment of acne vulgaris.

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}

Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor's proposed agenda

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:	May 09, 2018 @ 9:00 am
Meeting Location:	White Oak Campus, Building 22 Room 1419
Application Number:	IND 125961
Product Name:	benzoyl peroxide and tretinoin cream, 3%/0.1%
Proposed Indication:	For the topical treatment of acne vulgaris
Sponsor:	Sol-Gel Technologies, Ltd.
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
David Kettl, MD, FAAP, Clinical Team Leader, DDDP
Roselyn E. Epps, MD, Clinical Reviewer, DDDP
Selena Daniels, PharmD, Team Leader , Clinical Outcomes and Assessments (COA)
Yasmin Choudry, MD, Reviewer, COA
Marilena Flouri, PhD, Biometrics Reviewer, DB3
Alifiya Ghadiali, PhD, Microbiologist, Division of Monoclonal Antibodies (DMA)
Marc Neubauer, Chemist, GHDB
Vidula Kolhatkar, PhD, Acting Clinical Pharmacology Team Leader, Office of New Drug Products (ONDP)
Yichun Sun, PhD, Chemistry, Manufacturing, and Controls Team Leader, ONDP
Youmin Wang, PhD, Chemistry, Manufacturing, and Controls Reviewer, Office of Process and Facilities (OPF)
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES

(b) (4), Clinical Consultant
(b) (4) Toxicologist, Nonclinical Consultant
(b) (4) Statistical Consultant
(b) (4), PRO Consultant
(b) (4) Clinical Consultant
(b) (4) CMC and Process Development Consultant

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 the meeting was to discuss CMC, nonclinical and clinical strategies to support the safety and efficacy of benzoyl peroxide and tretinoin cream in the Phase 3 study and 505(b)(2) NDA.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 06/10/2015 PIND Meeting

We have sent the following correspondences:

- 03/02/2016 Study May Proceed Letter
- 04/12/2016 Advice Letter

2.0 DISCUSSION

2.1. Regulatory

There were no regulatory questions submitted for this meeting.

2.2. Chemistry, Manufacturing and Controls (CMC) and Nonclinical

(b) (4)

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(b) (4)

[redacted]

2.3. Nonclinical

Question 15:
Does the Agency agree that the proposed 28-day dermal study is adequate to qualify the individual unknown tretinoin related compound?

FDA Response to Question 15:
We agree that the proposed 28-day dermal study in minipigs with Vehicle and E-BPO/E-ATRA Cream (with enhanced degradants) containing a minimum of 2% of the unknown tretinoin related compound is adequate to qualify the individual unknown tretinoin related compound.

Question 16:
Does the Agency agree that proposed phototoxicity study in rabbits is adequate to support initiation of the Phase 1 photosafety study in humans?

FDA Response to Question 16:
We agree that testing the clinical formulation in the proposed phototoxicity study in rabbits is adequate to support initiation of the Phase 1 photosafety study in humans. Additionally, as per ICH S10 Photosafety Evaluation of Pharmaceuticals, testing the active ingredient in the 3T3 NRU-PT model or the clinical formulation in a reconstructed human skin model is also adequate.

Question 17:
Based on the minor differences between the toxicology and clinical drug product, does the Agency agree that the completed 13-week dermal toxicology study is adequate and does not need to be repeated?

FDA Response to Question 17:
Based on the minor differences between the toxicology and clinical drug product, we agree that the completed 13-week dermal minipig study is adequate and does not need to be repeated.

Question 18:
Does the Agency agree that no further nonclinical studies are needed to support a 505(b)(2) NDA?

FDA Response to Question 18:
If you are able to establish an adequate clinical bridge to a listed drug containing all-trans retinoic acid and if a juvenile toxicity study is determined by the Agency to not be necessary (see answer to Question 19), we agree that no further nonclinical studies are needed to support a 505(b)(2) NDA.

Question 19:
Does the Agency agree that a juvenile toxicology study is not needed to support use of E-BPO/E-ATRA Cream in children above 9 years of age?

FDA Response to Question 19:
We agree that if no significant systemic absorption of the active ingredients is determined during Agency review of a maximal clinical use study conducted in adults and children 12-17 years of age, then a juvenile toxicology study is not needed to support the use of E-BPO/E-ATRA Cream in children above 9 years of age.

2.4. Clinical Pharmacology

Question 30:
Does the Agency agree with the maximal use PK study design?

FDA Response to Question 30:
You proposed to enroll subjects who will have at least 20 and not more than 50 inflammatory lesions (papules, pustules) and at least 25 and not more than 100 non-inflammatory (open and closed comedones) lesions on the face at baseline. We recommend that you do not set upper limits for the lesions on the face for the enrolled subjects. Furthermore, we recommend that you enroll subjects within the upper range of disease severity as anticipated in your Phase 3 trials and proposed product labeling.

Question 31:
Since the Reference Listed Drug (RLD), Retin-A® (tretinoin) Cream, 0.1% (NDA 017579), is approved for use in children 12 years of age and older, does the Agency agree that it is acceptable to only include a group of children ages 12 and above in the RLD arm of this study?

FDA Response to Question 31:
Your proposal to include children ages 12 and above in the listed drug arm appears reasonable.

Question 32:
Dose the Agency agree that children between 9 to 12 years of age are eligible patients if they have an IGA score of 2 or above while in adults and children 12 years of age and older are eligible patients if they have an IGA score of 3 or above?

FDA Response to Question 32:
In the maximum use PK study, we recommend that you make efforts to enroll subjects within the upper range of disease severity for this lowest age group (i.e. 9 years to < 12 years). See additional comments in FDA Response to Question 33.

Question 33:
Does the Agency agree with the sample size of 3 patients in the 9 to 12 years of age group to receive only E-BPO/E-ATRA Cream?

FDA Response to Question 33:
In the maximum use PK study, the sample size of only 3 subjects within the lower age range of 9 years to < 12 years of age is small. We recommend that you make additional efforts to enroll sufficient number of subjects within the lowest age range. In your NDA, provide a summary of pharmacokinetics parameters in subjects within the lowest age range (i.e. 9 years to < 12 years) and 12 years and older.

Question 34:
Does the Agency agree that it is acceptable to use Body Surface Area (BSA) to calculate the amount of drug that will be applied to the surface of the skin?

FDA Response to Question 34:
Your proposal of recording the BSA to be treated is reasonable; however, you proposed to apply the drug to the cheeks, forehead, nose, chin, shoulders, and back. We recommend that you also apply the drug product to upper chest in addition to the areas that you proposed without setting an upper limit on the amount of drug to be applied. Drug should be applied in sufficient amount to cover the aforementioned body surface areas.

Question 35:
Dose the Agency agree that based on the bioanalytical method development report, a lowest limit of quantitation (LLOQ) for tretinoin in the blood samples of 0.5 ng/mL and a LLOQ for all other tretinoin metabolites of 1.0 µg/mL is acceptable?

FDA Response to Question 35:
The bioanalytical method should be sensitive enough to help produce enough quantifiable concentrations to permit relative bioavailability (BA) assessment between your product and the listed drug. Since relative BA assessment would help support a clinical bridge, obtaining reliable PK assessment would be pertinent. Lack of bioanalytical sensitivity causing non-quantifiable PK might impact your ability to establish a clinical bridge with the listed drug using relative bioavailability approach.

Question 36:
Does the Agency agree that quantification of the (b) (4) impurity in the maximal use PK study is not needed?

FDA Response to Question 36:
Clarify whether (b) (4) is an impurity contained in your product. We recommend that you measure the (b) (4) because it is (b) (4) (b) (4) (b) (4)

2.5. Clinical/Biostatistics

Question 20:
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 20:
Yes, assuming that the systemic exposure of tretinoin observed in your maximal use PK trial does not exceed that observed for other marketed topical tretinoin products. If there is higher systemic exposure, additional safety data may be necessary and this may impact the utility of your proposed clinical bridge.

Question 21:
Does the agency agree that based on the comparability of the Phase 2 and Phase 3 E-BPO/E-ATRA Cream formulations, only one Phase 3 study is required to support a 505(b)(2) NDA for E-BPO/E-ATRA Cream?

FDA Response to Question 21:
Yes, assuming that the systemic exposure of tretinoin observed in your maximal use PK trial does not exceed that observed for other marketed topical tretinoin products. If there is higher systemic exposure, additional safety data may be necessary.

See the 505(b)(2) Regulatory Comments under section 3.0 Administrative Comments.

Generally, we recommend two adequate and well-controlled trials (of appropriate design with endpoints agreed upon with the Agency) to establish efficacy and safety for a drug product. To establish an efficacy claim based on a single trial, the results need to be statistically robust and consistent across subgroups and centers, among other criteria. For robust statistical findings, the trial should be powered for the recommended co-primary endpoints using a two-sided alpha much less than the customary 0.05. Refer to the guidance for industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, for additional discussion about relying on a single trial to provide evidence of effectiveness.

Question 22:
Does the Agency agree that the selected dosage strength for the Phase 3 clinical study, E-BPO/E-ATRA Cream, 3%/0.1%, is appropriate?

FDA Response to Question 22:
In general, your proposed dosage strength appears reasonable. While results for change and percent change of inflammatory and noninflammatory lesions are similar for both combination products S6G5T-3 and S6G5T-1, the response rates for success on the IGA are 40% and 27%, respectively. This makes interpretation of study findings and selection of the dose difficult. Ultimately, selection of the dose to be evaluated in Phase 3 trial(s) is your choice.

Question 23:
Does the Agency agree that the selected formulation for Phase 3 (E-BPO/E-ATRA Cream, 3%/0.1%) demonstrated numerical superiority over its monads in the Phase 2 study and that each

component made a contribution to the claimed effects; therefore, the Phase 3 study can include a comparison of only E-BPO/E-ATRA Cream, 3%/0.1% and its Vehicle Cream?

FDA Response to Question 23:
The selected formulation did not demonstrate numerical superiority for the non-inflammatory lesions against one of the two monads (E-ATRA 0.1%), in which arm the dropout rate was large (25%). We have concerns regarding the large dropout rate in your Phase 2 trial and the impact of the method for handling the missing data on interpreting study findings. Also, we are concerned about the impact of deleting data for Center 27. As one of the objectives of the clinical trial is to establish the contribution of the monads, we are requesting the efficacy results for the completers only. Also, you should provide the efficacy results for Center 27.

Meeting Discussion
The sponsor inquired whether the Agency would consider the completed Phase 2 trial as one of the pivotal trials required to support labeling and approval of their product, and the utility of this data for consequently powering their future Phase 3 trial using significance level of 0.05. In response, the Agency re-iterated their concerns about the large dropout rate that occurred in the Phase 2 trial, which impacts the interpretation of the study findings, and thus, the future Phase 3 trial should be powered using a lower significance level than 0.05.

The Agency referred to the large dropout rate in the completed Phase 2 trial, and since the majority of dropout was due to 'lost to follow-up', the Agency re-iterated the comment that for proper interpretation of study findings, it's important to have a study design and conduct to minimize the occurrence of missing data

The sponsor inquired whether their future Phase 3 trial can investigate the efficacy of both combination products (i.e., S6G5T-3 and S6G5T-1). In response, the Agency noted that this is the sponsor's choice, provided that adjustment for multiplicity is pre-specified to control the Type I error rate

Question 24:
Does the Agency agree that the proposed secondary efficacy endpoint at Weeks 4, 8 and 12 will support the efficacy claim?

FDA Response to Question 24:
(b) (4)

You listed many secondary endpoints and some are assessed at different time points. You may assess treatment effect at your proposed primary timepoint, as well as at each previous timepoint you specify, provided that you adjust for multiplicity. In addition, endpoints that rely on Patient Reported Outcomes (PROs) need to be validated and a clinically meaningful threshold level needs to be identified for treatment response prior to using such an endpoint in the Phase 3 trials.

Question 25:

Does the Agency agree that no blood tests and ECG measurements are required in the Phase 3 study?

FDA Response to Question 25:
Yes.

Question 26:
Does the Agency agree with the proposed sample size for the single, pivotal, Phase 3 clinical study?

FDA Response to Question 26:
You powered your Phase 3 trial using a two-sided alpha of 0.05 for the co-primary endpoints. For robust statistical findings based on a single trial, the trial should be powered for the co-primary endpoints using a two-sided alpha much less than the customary 0.05.

Additional Statistical Comment:
With the large dropout rates in your completed Phase 2 trial, interpretation of findings of the trial will be driven by the method of handling missing data. For your future clinical trial(s), as there is no one single method that is appropriate for handling missing data, all efforts should be made at the design phase and during the conduct of the trial to reduce the occurrences of missing data. While multiple imputation may be reasonable for certain type of missing data (e.g., missing at random) we encourage you to plan other sensitivity analysis for handling missing data, including the tipping point analysis to ensure that efficacy results are not driven by the method of handling missing data.

Question 27:
Does Agency agree that PRE-FACE (AID and ASD) is a content valid questionnaire (i.e., the questionnaire measures the signs, symptoms and impact concepts that are relevant to acne and important to patients with the condition and to which respondents are able to easily interpret and provide meaningful responses) and capable of generating reliable and construct-valid scores that are sensitive to change in the target patient population?

FDA Response to Question 27:
While the PRE-FACE captures concepts consistent with the literature and expert input, the results from your qualitative study does not indicate whether the included concepts in this instrument are the most important and relevant to patients. Clarify whether you asked patients to identify the most important and bothersome acne symptoms. And if so, please provide the findings from this exercise.

Additionally, the qualitative findings indicate that there were interpretation issues with this instrument. For example:

- Attribution of the concept to the incorrect cause (i.e., participant stated they experienced the concept of redness, but not due to acne), and interpretation of the concept that did not align with the developers' definitions.

- Sixty percent (n=12/20) of the interview participants did not have a clear understanding of item 3 (whiteheads). Ten participants (50%) interpreted "whiteheads" as pus-filled pimples or cysts (as opposed to small, non-inflammatory raised facial lesions capped with white to flesh-colored skin debris), and two participants (10%) reported that they were unfamiliar with and unable to define the concept. It is unclear why despite a fair number of participants having difficulty with interpretation, only few (n=4) suggested modifications to the items and ultimately, no modifications were made to the PRE-FACE.

- Twenty-five percent (n= 5/20) of the interview participants reported that one or more of the PRE-FACE items were redundant. All five participants reported that various combinations of Items 5, 6, and 7 ("embarrassed," "self-conscious," and "sad," respectively) asked about the same concept. Five participants (25%) reported that an item should be considered for removal from the PRE-FACE. Four participants (20%) suggested removing Item 7 (Sad), and one participant (5%) suggested removing Item 5 (Self-conscious).

Although you provided evidence to support the response options for the PRE-FACE, it is unclear how a person rates the severity of "pimples," "blackheads," and "whiteheads," on a 0-10 response scale (0= no pimples/blackheads/whiteheads, 10=pimples/blackheads/whiteheads as bad as you imagine). It is unclear whether the basis of the patients' rating is related to lesion size, number of lesions, or other lesion characteristics. Transcripts were not submitted to investigate how patients interpreted the response scale. Please provide this information if available.

Because of the concerns outlined above, we believe that the content validity of the PRE-FACE is questionable at this time

Meeting Discussion:
The sponsor clarified that they did not ask patients to rank the most bothersome acne symptoms and impacts. However, the sponsor states that they have information to support the symptoms and impacts included in the PRE-FACE are the most important to patients. The Agency requested that the sponsor submit this information.

The sponsor suggested a new approach to their PRO endpoints. The sponsor proposed to utilize two single items from the PRE-FACE as secondary endpoints: Item 1 (pimples) and Item 5 (embarrassment). The Agency stated that we are open to the sponsor's proposal however, we would like to review the supporting data first and sponsor justification and data to support this should be submitted to the IND.

Question 28:
Does the Agency agree that the PRE-FACE (ASD and AID) is appropriate for use among individuals 9 to 11 years of age with moderate to severe acne vulgaris?

FDA Response to Question 28:
At this time, we cannot agree without additional information. The qualitative report does not address how 9-12 year old patients describe the symptoms/signs (such as whiteheads,

blackheads, redness) and whether these symptoms/signs are as important/relevant/bothersome to this age group. Similarly, the report does not address whether the impacts are important/relevant/bothersome to this subgroup. See FDA Response to Question 25.

Question 29:
Does the Agency agree that the PRE-FACE key secondary endpoints support conclusions about treatment benefit?

FDA Response to Questions 29:
No, you will need to address the concerns outlined in the FDA Response to Questions 25 and 26.

Additional comments-Clinical Outcome Assessments:
It is important to note that it is not possible to interpret the quantitative findings without first having confidence that the instruments are content valid (i.e., the instrument is measuring the concept(s) of interest). Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

Question 37:
Does the Agency agree that no pediatric clinical studies will be required in children less than 9 years of age?

FDA Response to Question 37:
Yes, we agree that excluding children less than 9 years from your clinical trials is reasonable. Any request for a deferral, partial waiver or waiver must be submitted with the Initial Pediatric Study Plan (iPSP) along with supporting information. See PREA Requirements under Administrative Comments for additional details.

Question 38:
Does the Agency agree that a request for a waiver from the requirement to conduct a long-term safety study for E-BPO/E-ATRA Cream is appropriate?

FDA Response to Question 38:
Yes, assuming that the systemic exposure of tretinoin observed in your maximal use PK study does not exceed that observed for other marketed topical tretinoin products. If there is higher systemic exposure, additional long term safety data may be necessary.

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* 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 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

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

SECURE EMAIL COMMUNICATIONS

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

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.

505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge"

(e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

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

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

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

- Other significant changes
- Proposed implementation date

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

4.0 ATTACHMENT

- Sponsor's proposed teleconference agenda

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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
08/17/2018