CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213478Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 137467

MEETING MINUTES

Nobelpharma Co., Ltd
c/o Dunn Regulatory Associates, LLC
Attention: Dana Dunn, MS
US Regulatory Agent
2709 Silkwood Court
Oakton, VA 22124

Dear Ms. Dunn:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sirolimus gel, 0.2%.

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2018. The purpose of the meeting was to discuss the development program for sirolimus gel, 0.2%.

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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796 - 1015.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy 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:	Pre-NDA
Meeting Date and Time:	December 3, 2018, 8:30 – 9:25 a.m. (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Room 1311 Silver Spring, Maryland 20903
Application Number:	IND 137467
Product Name:	sirolimus gel, 0.2%
Proposed Indication:	For the Treatment of facial angiofibromas associated with tuberous sclerosis complex (TSC)
Sponsor Name:	Nobelpharma Co., Ltd.
Meeting Chair:	Jill A. Lindstrom, MD
Meeting Recorder:	Mimi Phan, PharmD

FDA ATTENDEES
Jill A. Lindstrom, MD, Deputy Director, Division of Dermatology and Dental Products (DDDP)
Patricia Brown, MD, Clinical Reviewer, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
John Dougherty, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Rebecca Hager, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) III
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
CAPT Mimi Phan, PharmD, US Public Health Service, Regulatory Project Manager, DDDP

SPONSOR ATTENDEES
Shigeki Shimasaki, Vice President and COO Nobelpharma, Co. Ltd
Masanori Osakabe, Executive Director Nobelpharma, Co. Ltd
Kenji Shimizu, Project Manager Nobelpharma, Co. Ltd
Sota Katayama, Clinical Lead Nobelpharma, Co. Ltd
Izumi Hamada, MS, Biostatistician Nobelpharma, Co. Ltd
Yuka Hasegawa, Sr. Regulatory Manager Nobelpharma, Co. Ltd

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1.0 BACKGROUND

Meeting Purpose:
The purpose of the requested meeting is to discuss the proposed clinical datasets to support the NDA for sirolimus gel, 0.2%.

Regulatory Correspondence History:

We have conducted the following meetings with you:

- February 21, 2018 – Pre-IND

We have sent the following correspondences:

- November 27, 2018 – Grant Fast Track
- November 27, 2018 – Deny Breakthrough Therapy Designation
- October 30, 2018 – Type C, Guidance, Written Request
- September 12, 2018 – Study May Proceed
- September 5, 2018 – Deny Fast Track
- August 23, 2018 – Deny Breakthrough Therapy Designation

INTRODUCTION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

2.0 DISCUSSION

2.1. Regulatory

Question 1:
Does the Division agree that the 505(b)(2) regulatory requirements have been met?

FDA Response to Question 1:
If you plan to submit a 505(b)(2) regulatory pathway application, you need to provide information to support a clinical bridge.

See FDA Response to Question 8 under section 2.4 Clinical Pharmacology.

Nonclinical data alone is not adequate to establish the clinical bridge.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. If you intend to rely on our finding for one or more listed drug(s), you should be aware that 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 that you rely on. 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.

Meeting Discussion:
The Sponsor noted that they have additional PK data from their completed long-term study, which they plan to submit.

The Sponsor proposed to conduct a relative bioavailability study to support their 505(b)(2 regulatory pathway. The Agency recommended the Sponsor submit a protocol for review prior to study initiation.

Question 2:
Does the Division agree that the drug could be approved under 21 CFR Part 312 Section E?

FDA Response to Question 2:
Clarify your question. We agree that your proposed drug product is eligible for Fast Track Designation. Refer to our November 27, 2018, Grant Fast Track letter.

Question 3:
Does the Division agree with the planned contents of the datasets for the NDA?

FDA Response to Question 3:
We agree that the current nonclinical package supports a potential NDA for NPC-12G gel and that SEND datasets are not required for the NDA submission. Refer to the Written Responses document sent to you on October 30, 2018 that granted your waiver request for conduct of a dermal carcinogenicity study.

Ideally, the long-term safety (LTS) study report would be complete at the time of NDA filing.

Present the results of the Phase 1/2 and Phase 3 trials separately (not pooled).

Additional Comments:

1. Submit Case Report Forms (CRFs) for all subjects.

2. Submit photographs for all subjects from each study visit.

3. In addition to the CRFs above, provide narratives for all deaths, serious adverse events (SAEs) regardless of causality, subjects who discontinued the study product due to adverse events (AEs), hypersensitivity reactions, and pregnancies. These narratives may also be included in the Clinical Study Reports (CSRs) with links to the narratives provided in the relevant sections of the Overview of Clinical Safety and Summary of Clinical Safety.

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 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 sorted as needed; however, if it is submitted as a PDF document, we request that it include both directions (verbatim -> preferred and preferred -> verbatim).

5. Include the full text version of any referenced articles.

6. The analyses of the Phase 1/2 and Phase 3 trials should include the following:

    - Separate presentation of the results of the Phase 1/2 and Phase 3 trials (not pooled).
    - Summary Table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term reported by ≥1% of subjects for individual trials
    - Summary Table of Treatment-Emergent Treatment- Related Adverse Events (Adverse Reactions) by System Organ Class and Preferred Term reported by ≥1% of subjects for individual trials
    - Case report forms (CRFs) and narratives with corresponding electronic links as discussed above.
    - 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.
    - If the product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120-day safety update.
    - Safety analyses in subgroups of subjects by sex, race, age group (>65 years versus < 65 years), and baseline severity.

- Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug

7. Provide in the 120-day safety update, a summary of information which was not submitted in the NDA including the following:

- A detailed description of any significant changes or findings in the safety profile.
- A description of any information that suggests a substantial change in the incidence of common, but less serious adverse event.
- A summary of worldwide experience of safety of the proposed drug including an updated estimate of use for the drug marketed in other countries.

If you wish to only submit results from the Phase 1/2, Phase 3, and long-term study of NPC-12G gel, it is acceptable to not include and ISE in the NDA submission.

Post Meeting Addendum:
For an NDA application, an ISE is required; however, as your Phase 1/2 and Phase 3 trials are of different designs and evaluate different formulations, present efficacy results from each trial separately and do not pool efficacy results across trials. See FDA Guidance for Industry, *Integrated Summary of Effectiveness* (https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf).

2.2. Clinical Pharmacology

Question 8:
Does the Division agree that no further clinical pharmacology studies are warranted for NPC-12G gel NDA submission?

FDA Response to Question 8:
We note that you have obtained only trough level PK assessment in your Phase 3 clinical trial conducted in Japanese population and full PK profile of your product was not assessed. Furthermore, it is not clear if the PK assessment was conducted under maximal use conditions. Refer to pre-IND meeting minutes (dated on 02/21/2018) for more information on how to design a maximal use study.

In addition, you have not conducted a relative bioavailability study with your product administered under maximal use conditions and the listed drug to support a clinical bridge. We recommend you address the clinical bridge between your product and the listed drug.

Meeting Discussion:
See meeting discussion in Question 1.

Post meeting addendum:
If the systemic exposure of your topical product under maximal use conditions is lower than the oral listed drug identified by you, then a TQT study is not needed per ICH E14.

2.3. Clinical/Biostatistics

Introductory Comments:
You conducted a Phase 1/2 study evaluating 3 doses of the OSD-001 gel formulation in 36 subjects (24 in the sirolimus groups, 12 in the placebo group) and a Phase 3 trial evaluating the NPC-12G gel 0.2% formulation in 62 subjects with angiofibromas as a part of tuberous sclerosis (30 in the sirolimus group, 32 in the placebo group) in Japan. The assessment of efficacy was based on improvement relative to baseline. You state that the primary endpoint in the Phase 3 trial was the composite improvement in size and color of the facial angiofibromas (AF) at Week 12 assessed using photographs by the Independent Review Committee (IRC); there were also at least 43 secondary endpoints listed in the SAP, including endpoints evaluated by a live investigator.

At the Pre-IND meeting with minutes dated 4/17/2018, the Agency commented on the need for well-designed and conducted clinical trials to establish efficacy including pre-specification of the statistical methodology. In the current submission:

1. You propose the use of the investigator assessment of improvements in AF size and redness as co-primary endpoints, where dichotomized improvement rates are used instead of the 6-point improvement scores, and success (improvement) includes the categories of "markedly improved" and "improved" and failure is all other categories.

2. You state that (b) (4)

3. You consider that the results from the Phase 3 trial meet the regulatory guidance for a single study in terms of consistency of the results across subgroups and robust study findings.

Your current submission includes a SAP for the Phase 3 trial that states it was prepared in December 2016 and last amended in February 2017, which is after the trial was conducted between December 2015 and October 2016. Your proposed endpoint for assessing treatment effect is based on improvement relative to baseline, however a mere improvement from baseline may not be sufficient for demonstrating a clinically meaningful treatment effect for establishing efficacy of your product. The requirement for consistency and robust statistical finings for a single pivotal trial is interpreted as persuasive statistical results for a clinically meaningful endpoint(s) based on pre-specified statistical methods usually using a significance level much smaller than 0.05.

Meeting Discussion:
The Agency emphasized the importance of information to support the establishment of clinical meaningful effect.

Question 1:
Does the Division agree that the Phase 3 study (NPC-12G-1) and the published clinical literature from controlled clinical trials, including the real-world evidence (RWE), demonstrates topical sirolimus as an effective treatment for facial AFs associated with TSC?

FDA Response to Question 1:
See Introductory Comments.

Regarding the Phase 3 trial, the provided results show a trend in favor of your product for the endpoint proposed by you; however, to make judgement about treatment effect of your product, provide:

- Clarification as to how your proposed endpoint, improvement from baseline, can be used to establish a clinically meaningful treatment effect.

- The original protocols as well as any revision detailing changes if any of the endpoint and statistical analysis plan.

- Clarification as to how change in lesion color and size are the key factors for evaluation of improvement from baseline and hence relevant for assessment of treatment effect and for interpretation of study findings.

Angiofibromas are benign tumors and for tumors, a clinically meaningful endpoint is complete disappearance of the tumor. Your primary efficacy outcome measure was defined as improvement in angiofibroma size and redness. It is unclear how the size was assessed (which objective measure was used). While the study results provided by you may be indicative of treatment benefit, provide evidence and data to indicate that the endpoint is clinically meaningful (e.g., translates into improvement in how a patient feels, functions, or survives.)

Address the disagreement in treatment effect between investigator (live) assessment and assessment by a panel with photographs. Because the primary endpoint is dependent on use of photographs, provide information about the standardized methods employed in the taking of photographs (e.g., distance, lighting, camera type). Provide photographs for all subjects.

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. 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., trade name(s)).

For a topical drug product, safety and efficacy may be impacted by dosage form and formulation. Provide a scientific rationale for how the clinical data from trials of products with different dosage forms and formulations are relevant to your product.

Meeting Discussion:
The Agency expressed concerns about assessment of improvement in the absence of having a baseline score. Whether the proposed improvement based on color and size is an acceptable endpoint would need clinical judgement. Knowledge of the subjects' baseline assessment is important for interpreting the study findings. Agreement in the assessment of the IRC members is critical for assessing the endpoints. Of note, the investigator assessment showed a smaller treatment effect based on improvement than that based on the IRC assessment.

The Sponsor inquired whether they could submit a statistical analysis plan (SAP) for the ISS. The Agency commented that the SAP for the Phase 3 trial was done in a post hoc manner. The Sponsor clarified that the SAP was signed one day prior to un-blinding the data.

Post Meeting Addendum:
In the NDA submission, provide details on how the Independent Review Committee (IRC) was conducted, including the individual member's ratings, and how the assessment of improvement was carried out. In assessing improvement, clarify the reference point such improvement was based on. Provide such baseline assessment along with the rating of improvement from each IRC member, and discuss how any disagreements between the IRC members' ratings were addressed. Explain any differences between the IRC vs. investigator assessments (e.g. photographs vs. live assessment, etc.). Discuss any training for the IRC members prior to making assessments for trial subjects, and provide a measure for the agreement of ratings, if any, during training and for the trial assessments.

Question 2a:
Does the Division agree that Phase 3 study, NPC-12G-1, fits FDA's definition of a well-designed and controlled trial that demonstrates efficacy of NPC-12G gel?

FDA Response to Question 2a:
See Introductory Comments and FDA Response to Question 1 under section 2.5 Clinical/Biostatistics.

Question 2b:
Does the Division agree that [redacted] (b) (4) to address multiplicity is reasonable and acceptable?

FDA Response to Question 2b:
We do not agree [redacted] (b) (4). Additionally, we note that the SAP lists the following secondary endpoints:

[redacted] (b) (4)

We do not agree that your secondary endpoints are adjusted for multiplicity. If your application is approved by the Agency, the endpoints that will be included in labeling will be a review issue and driven by clinical considerations.

Question 3:
Does the Division agree that analysis of the Phase 3 (NPC-12G-1) data using investigator scores and other endpoints could serve as the basis of approval for NPC-12G gel?

FDA Response to Question 3:
The investigator performed live assessment using a six-category comparative scale for determining change in redness and size of AF as a secondary endpoint. Provide information on how the assessment of change in size was performed and whether an objective measure was used.

See FDA Response to Question 2b under section 2.5 Clinical/Biostatistics about multiplicity issues related to this endpoint.

Question 4:
Does the Division agree that the single pivotal trial could be supportive of filing and acceptance of an NDA for NPC-12G gel?

FDA Response to Question 4:
See Introductory Comments and Response to Question 1 under section 2.5 Clinical/Biostatistics.

Question 5:
Does the Agency agree that the current NPC-12G gel safety database program is adequate to support an NDA filing?

FDA Response to Question 5:
The safety database needed depends upon the safety signals identified during your development program. Ultimately, the adequacy of your safety database will be a review issue.

Per the draft guidance for industry, *Rare Diseases: Common Issues in Drug Development*

> "There is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease. The number of patients to establish effectiveness and safety is determined on a case-by-case basis, taking into consideration the persuasiveness of the data (e.g., comprehensiveness and quality), the nature of the benefit provided (or expected in the case of surrogate endpoints), the length of treatment or exposure, the patient population that would be treated after marketing approval, and the concern for potential of harm from the treatment. Treatment duration should also be appropriate for the disease under study (e.g., chronic as compared to acute conditions). When conducting a benefit-risk assessment for a drug for a serious or life-threatening illness, FDA also recognizes that greater risks may be accepted for a treatment that is an advantage over available therapy."

Question 6:
Does the Division agree that NPC-12G gel data collected in the Japanese population is relevant to the U.S. population?

FDA Response to Question 6:
We expect that sponsors enroll participants who reflect the demographics for clinically relevant populations with regard to age, gender, race, and ethnicity; see Guidance for Industry and Food and Drug Administration Staff, *Collection of Race and Ethnicity Data in Clinical Trials.* In your

NDA, provide a scientific discussion to address the applicability of data collected in the Japanese population to the US population; see *ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data*.

Question 7:
Does the Division agree that the completed studies are adequate to assess dermal safety and that RIPT and CIST studies are not required for the NDA submission?

FDA Response to Question 7:
It appears that you identified signals for irritant and allergic contact dermatitis during development. We recommend you address these risks in your application through careful analysis of safety data for your product, supplemented by review of literature and relevant databases for the ingredients in your product. Clarify whether your product absorbs light in the UVB/UVA/VIS spectrum (290 nm – 700 nm).

Question 9:
Does the Division agree that it is acceptable to file the NDA with the electronic datasets as currently available and conversion to CDISC is not necessary?

FDA Response to Question 9:
As your studies were initiated prior to December 2016, you are not required to be CDISC compliant. Note, however that the datasets should be submitted in SAS transport format (.xpt).

Ensure that the data define files are clearly documented and that the analysis datasets include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study reports.

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

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 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.

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* and *Pregnancy and Lactation Labeling Final Rule* 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.
- 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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: http://www.fda.gov/ectd.

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 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

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 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), 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 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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/

JILL A LINDSTROM
06/11/2019 01:49:07 PM