

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216632Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 131347

MEETING MINUTES

Bausch Health Americas, Inc.
Attention: Sean Humphrey
Director, Global Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Mr. Humphrey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for clindamycin phosphate, benzoyl peroxide, adapalene (IDP-126) gel, 1.2%/3.1%/0.15%.

We also refer to the teleconference between representatives of your firm and the FDA on April 27, 2022. The purpose of the meeting was to discuss the development program for IDP-126.

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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosures:

- Meeting Minutes
- Sponsor Response to Meeting Preliminary Comments



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 27, 2022, 1:30 PM- 2:30 PM EST
Meeting Location: Teleconference

Application Number: 131347

Product Name: IDP-126
Proposed Indication: treatment of acne vulgaris (acne) in patients (b) (4) years of age and older.

Sponsor Name: Bausch Health Americas, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Amy Weitach, DO, MS, Clinical Team Leader, DDD
Sherry Zhou, MD, MSc, Clinical Reviewer, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Soo Hyeon Shin, PharmD, PhD, Clinical Pharmacology Reviewer, DIIP
Nina Ni, PhD, Product Quality Assessor, Division of New Drug Products II (DNDD II)
Bryan Ericksen, PhD, Biopharmaceutics Reviewer, Division of Biotechnology/Office of New Drug Products
Marijke Koppenol-Raab, PhD, Microbiology Reviewer, Division of Microbiology Assessment II
Kathleen Fritsch, PhD, Biometrics Reviewer, Division of Biometrics III
Kenya A. Brothers, PhD, Product Jurisdiction Officer/Center for Drug Evaluation and Research/Office of Executive Programs
Strother D. Dixon, Senior Regulatory Health Project Manager, Division of Regulatory Operations for Dermatology and Dentistry

SPONSOR ATTENDEES

Robert Israel, Senior Vice President, Medical and Clinical Affairs
RK Pillai, Vice President, Dermatology Development
Alan Traettino, Vice President, Regulatory Affairs
Shankar Swaminathan, Exec. Director, Regulatory CMC
Arturo Angel, Exec. Director, Formulation and Process Development

Linda Galbier, Exec. Director, CMC Regulatory Affairs
William Jo, Exec Director, Nonclinical
John Lahey, Exec Director, Clinical Services
Varsha Bhatt, Sr. Director, Clinical Services
Susan Harris, Sr. Director, Biostatistics
Shruti Sahay, Sr. Director, Analytical Sciences
Sean Humphrey, Sr. Director, Global Regulatory Affairs
Sateesh Kandavilli, Director, Formulation Development
Yen Nguyen, Associate Director, CMC Regulatory Affairs
Justin Forsman, Scientist III, Analytical Sciences
Manushi Patel, Manager, Project Management
Carla Sanders, Manager, Regulatory Affairs

1.0 BACKGROUND

The Sponsor is developing IDP-126 Gel, containing clindamycin phosphate, benzoyl peroxide (BPO), and adapalene for the treatment of acne vulgaris (acne) in patients (b) (4) years of age and older.

The Sponsor is formulating IDP-126 Gel by adding adapalene 0.15% (b) (4)

The development program was designed to support an original 505(b)(2) NDA with ownership and right of reference to NDA 050819 (Acanya gel) and NDA 050756 [Benzacilin (clindamycin phosphate and benzoyl peroxide) gel] for characterizing the nonclinical safety, and the clinical safety and efficacy of clindamycin phosphate and BPO in the treatment of acne. In addition, the Sponsor proposed a clinical bridge to NDA 207917 [Epiduo Forte (adapalene and benzoyl peroxide) gel] for characterizing the systemic exposure and safety of IDP-126 gel relative to Epiduo Forte gel.

The purpose of this meeting is to discuss the original NDA submission of IDP-126. The Sponsor seeks FDA's feedback on the overall organization of the electronic common technical document (eCTD) for the NDA, with focus on addressing specific questions related to filing and format, and to identify any additional information necessary to support the submission and review of the marketing application.

Regulatory History:

We have had the following meetings with you:

- November 19, 2020 - Guidance
- August 28, 2019 - End of Phase 2
- October 5, 2016 - Pre-IND

We have sent the following correspondences:

- March 25, 2021 - Pediatric Study Plan Initial Agreement

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- [REDACTED] (b) (4)
- January 17, 2020 - Advice
- August 8, 2017 - Study May Proceed

FDA sent Preliminary Comments to Bausch Health Americas, Inc. on April 22, 2022.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

2.2. Nonclinical

Question 8:

The IDP-126 Gel nonclinical development program was agreed upon with the Agency at the EOP2 meeting. For the drug product, IDP-126 Gel, the Sponsor conducted repeat dose toxicity and local tolerance studies to characterize the local and systemic toxicity of the novel drug combination. Additionally, the Sponsor will reference data from the ACANYA Gel and BENZACLIN Gel marketing applications for clindamycin and BPO data, and rely on the Agency's prior findings of safety for adapalene, by establishing a clinical bridge to the LD, EPIDUO FORTE Gel (NDA

207917). The results of the Phase 1 maximal use PK bridging study (V01-126A-501) demonstrated comparative bioavailability of adapalene to the LD.

- a. The Sponsor submitted the final report to the IND for the pivotal 3-month dermal minipig toxicity study with a 1-month recovery period prior to the initiation of the Phase 3 studies. Does the Agency agree that this study adequately characterizes the toxicity profile of IDP-126 Gel and that no additional studies with IDP-126 Gel will be required for the 505(b)(2) NDA?
- b. Assuming that a clinical bridge to the LD is established, does the Agency agree in principle that the nonclinical program is sufficient to support a 505(b)(2) NDA for IDP-126 Gel and that no additional toxicity studies will be required?

FDA Response to Question 8a:

We agree.

FDA Response to Question 8b:

We agree.

2.3. Biostatistics

Question 9:

The datasets for the following clinical studies will be included in the NDA in Clinical Data Interchange Standards Consortium (CDISC) format:

- V01-126A-301 (Phase 3 safety and efficacy)
- V01-126A-302 (Phase 3 safety and efficacy)
- V01-126A-202 (Phase 2 safety and efficacy bridge to EPIDUO FORTE Gel)
- V01-126A-201 (Phase 2 parallel group, safety and efficacy study)
- V01-126A-501 (Phase 1 maximal use PK bridge to EPIDUO FORTE Gel)
- V01-126A-101 (21-day cumulative irritation)
- V01-126A-102 (RIPT)

Does the Agency agree with the provision of the files in this format?

FDA Response to Question 9:

We agree that the datasets for the above studies should be submitted in Clinical Data Interchange Standards Consortium (CDISC) [both SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model)] format. Submit datasets in SAS (Statistical Analysis System) transport format (.xpt). The analysis datasets should include all variables needed for conducting the analyses included in the study report.

- a) Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms

- for derived variables (including source variables used), and descriptions for the codes used in factor variables.
- b) Include statistical programs for the key primary and secondary analyses, including programs for the multiple imputation.
 - c) Include all protocols (including protocol amendments) and statistical analysis plans.
 - d) Include an annotated case report form. If any data is collected via electronic data capture rather than directly on the case report form (CRF), include annotated screen shots of the electronic data capture system.

Question 10:

Statistical analyses of the safety data for the Phase 3 studies V01-126A-301 and V01-126A-302 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Safety (ISS). The ISS text document will be placed into Module 2, Section 2.7.4, with the appendices and datasets provided in Module 5. As per Option D in the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*, each section of the ISS will refer the reader to the appropriate section where the remainder of the ISS is located within the NDA.

- a. Does the Agency agree with the statistical analysis plan for pooling of safety data for the Phase 3 clinical studies?
- b. Does the Agency agree with the plan to provide the ISS text document in Module 2, Section 2.7.4 and datasets in Module 5, Section 5.3.5.1?

FDA Response to Question 10a:

Analyses based on integrated data from the two phase 3 studies are one component of the ISS. Additional data pools that include the phase 2 trials also may be appropriate and analyses based on these pools should be described in the ISS statistical analysis plan. To maintain the randomized comparisons of the individual trials and to avoid confounding, stratification by trial is recommended, rather than crude pooling.

For subgroup analyses based on age, you have proposed groupings based on the median age (<median versus $\geq$ median) and <18 years versus $\geq$ 18 years. In addition to these groupings, we recommend <12 years versus 12 to <18 years versus $\geq$ 18 years.

FDA Response to Question 10b:

If you meet the size and complexity limitations for the ISS as described in the guidance, it is acceptable to include the text summary in Section 2.7.4 and appendices and datasets in Section 5.3.5.1.

Question 11:

Statistical analyses of the efficacy data for the Phase 3 studies V01-126A-301 and V01-126A-302 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Efficacy (ISE). The ISE text document will be placed into Module 2, Section 2.7.3 with the appendices and datasets provided in Module 5. As per Option D in the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*, each section of the ISE will refer the reader to the appropriate section where the remainder of the ISE is located within the NDA.

- a. Does the Agency agree with the statistical analysis plan for pooling of efficacy data for the Phase 3 clinical studies?
- b. Does the Agency agree with the plan to provide the ISE text document in Module 2, Section 2.7.3 and datasets in Module 5, Section 5.3.5.1?

FDA Response to Question 11a:

Analyses based on integrated data from the two phase 3 studies are one component of the ISE. Refer to guidance for industry: *Integrated Summary of Effectiveness* (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summary-effectiveness>) for additional information on what the ISE should include. To maintain the randomized comparisons of the individual trials and to avoid confounding, we recommend stratification by trial rather than crude pooling.

For subgroup analyses based on age, you have proposed groupings based on the median age (<median versus $\geq$ median) and <18 years versus $\geq$ 18 years. In addition to these groupings, we recommend <12 years versus 12 to <18 years versus $\geq$ 18 years.

FDA Response to Question 11b:

If you meet the size and complexity limitations for the ISE as described in the guidance, it is acceptable to include the text summary in Section 2.7.3 and appendices and datasets in Section 5.3.5.1.

2.4. Clinical

The clinical development plan for IDP-126 includes 7 clinical studies:

- Study **V01-126A-101** was a completed 21-day cumulative irritation study.
- Study **V01-126A-102** was a RIPT study.
- Study **V01-126A-201** was a completed Phase 2 efficacy and safety study comparing IDP-126 Gel with its active components and vehicle. (9 years and older)
- Study **V01-126A-202** is an ongoing clinical **bridging** study to

evaluate the safety and efficacy of IDP-126 Gel relative to its vehicle and EPIDUO FORTE Gel. (12 years and older)

- Study **V01-126A-501** was a completed pharmacokinetic (PK) **bridging** study between IDP-126 Gel and EPIDuo Forte Gel in (9-16 yo, PK maximal use study) (page 41 of briefing package)
- Studies **V01-126A-301 and V01-126A-302** were two identical Phase 3 studies to evaluate the efficacy and safety of IDP-126 Gel in the treatment of acne vulgaris. (9 years and older)

Question 12:

The bridging strategy to EPIDUO FORTE Gel was agreed upon with the Agency at the pre-IND meeting held 05 October 2016 and again at the EOP2 meeting held 28 August 2019. The program includes a completed PK bridging study, V01-126A-501, and an ongoing safety and efficacy bridging study, V01-126A-202. The results for Study V01-126A-501 summarized within this briefing package suggest an adequate clinical PK bridge has been established.

Does the Agency agree that the results from the PK bridging study are adequate to establish a clinical PK bridge to EPIDUO FORTE Gel and that, with efficacy and safety results demonstrating an adequate clinical bridge at the conclusion of Study V01-126A-202, the study program will allow for a successful 505(b)(2) NDA pathway for IDP-126 Gel?

FDA Response to Question 12:

The bridging strategy appears adequate for filing. However, the adequacy of the study will be a review issue.

Question 13:

Based on the completion of the clinical program as detailed within this briefing package, does the Agency agree that the clinical program is adequate to support approval of IDP-126 Gel with an indication for the topical treatment of acne vulgaris?

FDA Response to Question 13:

The clinical development program of IDP-126 gel consists of 7 clinical studies mentioned above. (b) (4)

The clinical program appears adequate for filing. However, the adequacy of the studies to support approval of IDP-126 gel will be a review issue.

Question 14:

A total of approximately 925 human subjects will have been exposed to at least 1 dose of IDP-126 Gel and will be include in the NDA submission as part of the safety

database. Of these, approximately 646 are subjects with acne who were treated with the to-be-marketed formulation of IDP-126 Gel.

Does the Agency agree that the total subject exposure is adequate to support approval of the NDA?

FDA Response to Question 14:

Your proposed total subject exposure appears reasonable if you can establish an adequate clinical bridge. (b) (4)

Question 15:

The Sponsor plans to provide Bioresearch Monitoring (BIMO) clinical data in the eCTD format. For each pivotal Phase 3 study, the following will be provided in Module 5, Section 5.3.5.4:

- BIMO study tagging file (STF), containing general study related information and specific clinical investigator information (if specific items are provided elsewhere in the submission, a location or link will be provided)
 - General study related information and specific clinical investigator information in tabular format (submitted in portable document format [PDF])
 - Data listing by study center in tabular format (submitted in PDF)
 - Data listings by study in tabular format (submitted in PDF)
- Site level data sets across studies (clinsite.xpt)

For each pivotal Phase 3 study, the following will be provided in Module 5, Section 5.3.5.1 (data listing datasets):

- Subject level data listings by study center (PDF)
- Define file (PDF)

Does the FDA agree to the eCTD location of the BIMO information that will be included in the original NDA?

FDA Response to Question 15:

We agree with the eCTD location of the BIMO information. In addition to the two phase 3 studies, include the above BIMO information for Study V01-126A-201.

Question 16:

For the 2 pivotal Phase 3 studies (V01-126A-301 and V01-126A-302), the

Sponsor plans to submit case report forms in Appendix 16.3 of the clinical study reports by study center and subject identifier. Case report forms for the following subjects will be submitted in the NDA:

- Deaths during the study(s)
- Other SAEs during the study(s)
- Discontinuations due to an AE during the study(s)

Does the Agency agree with the case report forms the Sponsor proposes to submit in the NDA for the pivotal Phase 3 studies?

FDA Response to Question 16:

In addition to case report forms, submit subject narratives for all deaths, serious adverse events, and discontinuations due to an adverse event (AE). Furthermore, provide CRFs and narratives for all pregnancies, hypersensitivity reactions, and severe AEs (Grade 4-5).

Also include the following data:

- the generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials
- CRFs for all severe AEs and for all subjects who discontinued from the studies for any reason
- Place a study's CRFs in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:
 - Electronic links for:
 - all serious AEs
 - all severe AEs
 - all patients discontinued regardless of reason
 - all deaths
 - CRFs should be referenced under the study in which it belongs and tagged as "case-report-forms" in that study's stf.xml file. CRFs that are not submitted should be readily available upon request.
- adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq 1\%$
- adverse event tables $\geq 1\%$ regardless of causality. Line listings for all safety data
- group means for irritancy safety study results.
- Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

In addition, include the CRFs and narratives for the above situations for Study V01-126A-201.

Meeting Discussion:

The Sponsor inquired whether the separate dermal safety studies which were conducted address the Agency's comments. The Agency stated that the application should contain a safety analysis of the active dermal safety assessments that were conducted in your phase 3 studies in addition to the clinical study reports for V01-126A-101 (Cumulative irritation test study) and V01-126A-102 (Repeat insult patch test study).

Question 17:

At the pre-IND meeting held 05 October 2016 and at the EOP2 meeting held 28 August 2019, a long-term study waiver was discussed, and FDA stated that a long-term safety study may not be required if an adequate clinical bridge is established. The safety and efficacy results from the Phase 2 bridging study (V01-126A-202) and the PK results from the Phase 1 PK bridging study (V01-126A-501) will provide evidence that the safety profile and systemic exposure of IDP-126 Gel is similar to EPIDUO FORTE Gel and, consequently, would not require a separate long-term safety study to support registration of IDP-126 Gel. In addition to the PK and safety and efficacy studies, a 21-day cumulative irritation study (V01-126A-101) established that the irritation profile of IDP-126 Gel is significantly less than that of EPIDUO FORTE Gel.

Does the Agency agree that, based upon the available PK data, and the efficacy and safety results of the ongoing clinical bridging study, an adequate clinical bridge will be established and an additional long-term safety study with IDP-126 Gel is not needed for a 505(b)(2) NDA approval?

FDA Response to Question 17:

Based on the safety profile demonstrated in clinical trials of IDP-126 el, results of the clinical bridging study, and the established safety profile of Epiduo Forte gel, it appears reasonable that a long-term safety study is not needed. The final determination of this issue will be made during review of the safety experience and PK data during the NDA review, (b) (4)

Question 18:

Adapalene formulated in DIFFERIN Solution, 0.1% has been approved for use since May 1996. In addition, adapalene formulated in EPIDUO and EPIDUO FORTE Gel has been approved and commercialized for use since December 2008 (EPIDUO Gel). Adapalene has been approved and commercialized for use since 1996, with no associated reported cardiac events of interest (eg, torsades de pointes and cardiac arrhythmia). The bioavailability of IDP-126 Gel has been shown to be similar to that of EPIDUO FORTE Gel based on the PK results from the Phase 1 bridging study that, when coupled with the lack of reported cardiac arrhythmias associated with

adapalene use, indicate a pro-arrhythmia risk is not anticipated with the use of IDP-126 Gel. In addition, *in vitro* hERG and electrocardiogram data in minipigs did not reveal any safety concerns. In the pre-IND and EOP2 meeting minutes, the FDA stated a TQT waiver is reasonable, provided that the systemic exposure from IDP-126 Gel is similar to the systemic exposure from EPIDUO FORTE Gel. Therefore, the Sponsor intends to request a waiver for conducting a clinical study with IDP-126 Gel to evaluate the potential for QT/QTc interval prolongation.

Does the Agency agree that a TQT study to assess the potential of QT prolongation with the use of IDP-126 Gel is not needed for NDA filing and approval?

FDA Response to Question 18:

Your plan to request a waiver for conducting a Thorough QT (TQT) study appears reasonable. Final determination will be made at the time of your NDA review.

2.5. Clinical Pharmacology

Question 19:

The Sponsor has completed a maximum use clinical PK study (V01-126A-501) in subjects aged 9 and above in order to establish a clinical PK bridge to the LD, EPIDUO FORTE Gel. A relative bioavailability assessment was conducted by calculating the ratio of the geometric means for adapalene C_{max} and AUC from IDP-126 Gel over those for EPIDUO FORTE Gel. The results of this analysis, as presented in this briefing package, demonstrate comparable bioavailability for IDP-126 Gel versus EPIDUO FORTE Gel.

Does the Agency agree that the comparative bioavailability data from Study V01-126A-501 is adequate to establish a clinical PK bridge between IDP-126 Gel and EPIDUO FORTE Gel?

FDA Response to Question 19:

Study V01-126A-501 appears adequate to provide data to examine a clinical PK bridge between IDP-126 gel and Epiduo Forte gel in subjects 12 years of age and older. The adequacy of the data will be a review issue.

2.6. Regulatory

Question 20:

The Sponsor proposes to submit the IDP-126 Gel NDA in eCTD format with a complete XML backbone. The proposed content for Modules 1-5 is provided in Section 1.6.2.12.7.

Does the Agency concur with the content and format of the NDA as outlined in this briefing package?

FDA Response to Question 20:

Forms 356h, 3397, and 3674 should be placed in Section 1.1 (Forms). The Proposed eCTD Table of contents for planned IND submission contains Form 356h, Form 3397, and Form 3674 in Section 1.1.2, 1.1.3 and 1.1.7 respectively.

Refer to the Comprehensive Table of Contents Headings and Hierarchy Section 1.1 Forms for more details.

Additional Biopharmaceutics Comments

You may consider developing an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for your drug product to be used systemically at release and during stability as an additional quality control parameter as well as for potential pre- and post-marketing bridging purposes. Refer to the *Scale-Up and Post-Approval Changes-Semisolid (SUPAC-SS)* guidance <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ss-nonsterile-semisolid-dosage-forms-scale-and-post-approval-changes-chemistry-manufacturing-for-developing-a-suitable-IVRT-method>.

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*.² 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.³

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ 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

² 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>.

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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).⁸ 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

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁸ 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>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov).⁹

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.

⁹ <http://www.regulations.gov>
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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.

4.0 ATTACHMENTS AND HANDOUTS

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

The Sponsor was provided the Meeting Preliminary Comments on April 22, 2022.
The Sponsor provided responses via the attached document on April 25, 2022.

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
05/27/2022 10:18:26 AM



IND 131347

MEETING MINUTES

Bausch Health Americas, Inc.
Attention: Sean Humphrey
Associate Director, Global Regulatory Affairs
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear Mr. Humphrey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IDP-126 (clindamycin phosphate, benzoyl peroxide, and adapalene) gel, 1.2%/3.1%/0.15%.

We also refer to the teleconference between representatives of your firm and the FDA on August 28, 2019. The purpose of the meeting was to discuss the development program for IDP-126 gel.

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 Dawn Williams, Regulatory Project Manager at (301)796-5376.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: August 28, 2019; 11:00 (EDT)
Meeting Format: Teleconference

Application Number: IND 131347
Product Name: IDP-126 (clindamycin phosphate, benzoyl peroxide, and adapalene) gel, 1.2%/3.1%/0.15%
Proposed Indication: For the topical treatment of acne vulgaris (acne) in patients (b) (4) years of age and older
Sponsor Name: Bausch Health Americas, Inc.

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Dawn Williams, BSN, Regulatory Project Manager, DDDP
Luke Oh, PhD, Acting Clinical Pharmacology Lead, Division of Clinical Pharmacology III (DCP III)
Soo Hyeon Shin, PhD, Clinical Pharmacology Reviewer DCP III
Mohamed Alesh, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Kathy Fritsch, PhD, Biometrics Reviewer, DB III
Donna Christner, PhD, API Branch Chief, Division of New Drug API, Branch II

SPONSOR ATTENDEES

Anya Loncaric, Senior Director, Clinical Services
Arturo Angel, Executive Director, Formulations and Process Development
E. Kwame Obeng, Vice President, CMC Regulatory Affairs
Ezra Lowe, Director, Clinical Pharmacology
Linda Galbier, Senior Director, Regulatory Affairs-CMC
RK Pillai, Vice President, Dermatology Development
Robert Kang, Senior Director, Data Management
Sean Humphrey, Associate Director, Global Regulatory Affairs
Shruti Sahay, Senior Director, Analytical Sciences, Lab Operations
Susan Harris, Director, Biostatistics
Varsha Bhatt, Director, Dermatology Development

William Jo, Senior Director, Nonclinical
Yen Nguyen, Senior Manager, Regulatory Affairs-CMC

(b) (4)

1.0 BACKGROUND

Regulatory Correspondence History

We have had the following meetings:

- October 5, 2016 Pre-IND

We have sent the following correspondences:

- August 8, 2017 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 18:

Does the Agency agree in principle with the Sponsor's plan to request a partial waiver to conduct clinical studies with IDP-126 Gel in pediatric subjects 0 to 8 years, 11 months of age?

FDA Response to Question 18:

A partial waiver may be acceptable for the conduct of clinical studies with IDP-126 Gel in pediatric subjects aged 0-8 years 11 months. You should discuss your plans for pediatric development in your initial pediatric study plan and include your rationale and adequate supporting information for any proposed waiver(s). Include your waiver request in the marketing application, along with your rationale and supporting information. Note the timeline for the pediatric study plan submission in the Administrative Comments below.

2.2. Chemistry, Manufacturing, and Controls

(b) (4)

(b) (4)

2.3. Nonclinical

Question 10:

Assuming a clinical bridge is established to the listed drug for adapalene, does the Agency agree that the existing body of nonclinical data from the referenced applications coupled with the completed IDP-126 Gel repeated dose and local tolerance studies are sufficient to support a new 505(b)(2) NDA for IDP-126 Gel?

FDA Response to Question 10:

You state that you have ownership and right of reference for Acanya Gel (NDA 050819) and BenzaClin Gel (NDA 050756). We agree that the existing body of nonclinical data from the referenced applications for Acanya Gel and BenzaClin Gel and your completed IDP-126 Gel repeated dose and local tolerance studies are sufficient to support a 505(b)(2) NDA submission for IDP-126 Gel if you are able to generate a clinical bridge to the listed drug (i.e., EpiDuo Forte Gel NDA 207197) for adapalene.

Question 11:

Does the Agency agree in principle that this study adequately characterizes the toxicity profile of IDP-126 Gel and that no additional studies with IDP-126 Gel will be required for the 505(b)(2) NDA, pending review of the final study report?

FDA Response to Question 11:

We acknowledge that you have completed a pivotal 3-month dermal minipig toxicity study with a 1-month recovery period to evaluate the local and systemic toxicity of

IDP-126 Gel. You state that the final report for this nonclinical study will be submitted to the IND prior to initiation of the Phase 3 study.

We agree that this nonclinical study appears acceptable to characterize the toxicity profile for IDP-126 Gel. The decision whether no additional nonclinical studies with IDP-126 Gel will be needed for the 505(b)(2) NDA submission will be dependent on review of the final study report; however, it appears reasonable that no additional nonclinical studies will be needed for the 505(b)(2) NDA submission.

Question 12:

Does the Agency agree that no nonclinical toxicology bridging studies will be needed for impurity safety characterization?

FDA Response to Question 12:

We acknowledge that you have completed the requested impurity profile comparison between the listed drug and IDP-126 Gel. You provided the methodology and summary of the results in the briefing package. We agree that no nonclinical bridging studies will be needed for impurity safety characterization based on the impurity profile comparison information that you provided in the briefing package.

2.3 Clinical Pharmacology

Question 17:

Does the Agency agree that the PK data are adequate to support the establishment of a clinical PK bridge between IDP-126 Gel and EpiDuo Forte Gel and the approval of an NDA for the proposed indication?

FDA Response to Question 17:

Based on your preliminary data from your ongoing relative bioavailability study between IDP-126 Gel and the listed drug EpiDuo Forte Gel, the systemic exposure of adapalene in subjects 12 years of age and older appears to be lower in subjects treated with IDP-126 Gel compared to subjects treated with EpiDuo Forte Gel. The adequacy of data to support a clinical bridge will be made at the time of NDA submission following detailed review of your study report as well as associated bioanalytical method validation and bioanalysis reports.

We acknowledge your plan to target at least 6 completers between 9 years to less than 12 years of age treated with IDP-126 Gel under maximal use conditions. From the limited PK data (n=3) in younger age group (9 years to less than 12 years) treated with IDP-126 Gel, the systemic exposure of your product appears to be higher than that observed in subjects 12 years of age and older. Provide a scientific rationale to support this observed increase in systemic exposure.

2.4 Clinical/Biostatistics

Question 13:

- a) Does the Agency agree that the complete clinical development plan proposed herein is sufficient to support substantive review and approval of IDP-126 Gel as indicated following the 505(b)(2) NDA regulatory pathway?
- b) Does the Agency agree that the numbers of subjects included in the clinical development plan are sufficient to adequately characterize the safety of IDP-126 Gel?

FDA Response to Question 13:

The proposed clinical development plan for IDP-126 Gel includes 7 clinical studies:

- o Study V01-126A-101 was a 21-day cumulative irritation study, which is now complete.
- o Study V01-126A-501 is an ongoing PK bridging study between IDP-126 Gel and EpiDuo Forte Gel.
- o Study V01-126A-201 is an ongoing Phase 2 efficacy and safety study comparing IDP-126 Gel with its active components and vehicle. Clinical conduct of this study is complete, while the data analysis, interpretation, and reporting are ongoing.
- o Study V01-126A-102 is a planned RIPT study.
- o Planned Phase 3 studies, V01-126A-301 and V01-126A-302, are presented in the meeting package.
- o Study V01-126A-202 is a planned additional clinical bridging study to evaluate the safety and efficacy of IDP-126 Gel relative to its vehicle and the listed drug.

The intent of the studies is to characterize the safety and efficacy of IDP-126 Gel, applied once daily for 12 weeks, in the treatment of acne in subjects 9 years of age and older. The clinical development plan is expected to include a minimum of 900 subjects exposed to the to-be-marketed formulation of IDP-126 Gel.

- a) The proposed development plan, once completed and if successful, would have reasonable assurance of filing. For a marketing application to be considered complete it must contain the information outlined in 21 CFR 314.50. We recommend that you request a pre-NDA meeting following the completion of trials intended to form the basis for a marketing application, and prior to the submission of a marketing application. During a pre-NDA meeting we would discuss the contents of a complete application.
- b) We typically use ICH-E1A guidelines to assess the clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. In the marketing application you may provide a scientific rationale to support that your safety database is sufficient to characterize the safety profile of IDP-126 Gel for the treatment of acne vulgaris.

Question 14:

- a) Does the Agency agree with the proposed clinical study design with 2 treatment arms for the pivotal Phase 3 studies?
- b) Does the Agency agree that the design, use of the EGSS, study endpoints, subject population, and inclusion/exclusion criteria for the Phase 3 clinical studies as described within the protocol are adequate to produce substantial evidence of efficacy and safety for the treatment of acne?
- c) Does the Agency agree that the planned statistical analyses for the Phase 3 clinical studies as described within the protocol are adequate to produce substantial evidence of efficacy and safety for the treatment of acne?

FDA Response to Question 14:

- a) Yes, conducting two Phase 3 studies of IDP-126 versus vehicle is acceptable.
- b) The design and endpoints proposed in the protocol are appropriate for assessing efficacy.
- c) The planned statistical analyses appear appropriate. Include full details for your analyses in the final protocol and statistical analysis plan.

Question 15:

The Sponsor intends to enroll up to 20% of the study population in the planned clinical studies from study centers located outside the US. At this time, the regions being evaluated for inclusion are Canada, Europe, and Latin America. Does the Agency agree?

FDA Response to Question 15:

We recommend that with the submission of the marketing application, you provide a rationale for assuming the applicability of foreign data to the U.S. population/practice of medicine.

Question 16:

Does the Agency agree that a long-term safety study with IDP-126 Gel is not needed for a 505(b)(2) NDA approval?

FDA Response to Question 16:

Your plan appears reasonable pending review of PK and safety data from the ongoing pharmacokinetic trial, (b) (4)

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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.³

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data

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 <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

Technical Conformance Guide,⁴ as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁵ 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.⁶ For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to

⁴ <https://www.fda.gov/media/88173/download>

⁵ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁶ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide⁷ (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.⁸ When submitting sample data sets, clearly identify them as such with SAMPLE STANDARDIZED DATASETS on the cover letter of your submission.

Additional information can be found at FDA.gov.⁹

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).

⁷ <https://www.fda.gov/media/88173/download>

⁸ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

- 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.

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 Resources¹⁰ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹¹

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.¹²

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.¹³

505(b)(2) REGULATORY PATHWAY

¹⁰ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹¹ <https://www.fda.gov/media/109533/download>

¹² <http://www.fda.gov/ectd>

¹³ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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).¹⁴ 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).¹⁵

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.

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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

¹⁴ 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>.

¹⁵ <http://www.regulations.gov>

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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*.¹⁶

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

¹⁶ <https://www.fda.gov/media/85061/download>

- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

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

UNITED STATES PATIENT POPULATION

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

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
09/20/2019 01:09:33 PM