CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213422Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127152

MEETING MINUTES

Drug Delivery Solutions Ltd
c/o Catalyst Regulatory Services, LLC
Attention: Toni Marie Nearing
Senior Director
7444 Dexter-Ann Arbor Road, Suite J
Dexter, MI 48130

Dear Ms. Nearing:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for calcipotriene betamethasone dipropionate cream, 0.005%/0.064%.

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2019. The purpose of the meeting was to discuss the development program for calcipotriene betamethasone dipropionate cream, 0.005%/0.064%.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 27, 2019 @ 8:30 a.m. (EDT)
Meeting Location:	White Oak, Bldg 22, Room1311
Application Number:	IND 127152
Product Name:	calcipotriene betamethasone dipropionate cream, 0.005%/0.064%
Proposed Indication:	Treatment of plaque psoriasis
Sponsor Name:	Drug Delivery Solutions, Ltd.
Meeting Chair:	Kendal Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Kevin Clark, MD, Clinical Reviewer, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Carmen Booker, PhD, Pharmacology Reviewer, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) 3
Jihye Ahn, PharmD, MS, Clinical Pharmacology Reviewer, DCP 3
Zhengfang Ge, PhD, Product Quality Reviewer, DNDP II, NDPB V
Sarrit Kovacs, PhD, Team Leader, Clinical Outcomes Assessment (COA)
Jing (Julie) Ju, PhD, Reviewer, COA
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES

Birgitte Vestbjerg, Director Clinical Operation, Drug Delivery Solutions/MC2 Therapeutics (DDS/MC2T)
Johan Selmer, Chief Medical Officer, DDS/MC2T
Franklin Okumu, CMC and Regulatory Affairs Consultant, DDS/MC2T
Jesper J. Lange, President and CEO, DDS/MC2T
Rikke Pordel Vind, VP Regulatory Affairs, DDS/MC2T

1.0 BACKGROUND

The purpose of the meeting is to discuss the planned NDA submission under the regulatory pathway of 505(b)(2) for calcipotriene betamethasone dipropionate cream, 0.005%/0.0064%.

Regulatory Correspondence History

We have conducted the following meetings with you:

- 12/19/2017 Final Written Response
- 08/17/2016 Guidance Meeting
- 10/07/2015 PreIND

We have sent the following correspondences:

- 08/30/2018 Advice
- 06/14/2018 Advice
- 03/28/2018 Advice
- 03/28/2018 Advice/Information Request
- 03/02/2018 Advice
- 12/29/2017 Advice/Information Request
- (b) (4)
- 07/06/2017 Study May Proceed
- 05/05/2016 Special Protocol Assessment – Non Agreement

2.0 DISCUSSION

2.1. Regulatory

Question 1: USPI
Does the Agency agree with the proposal to include an annotated comparison of the label for MC2-01 cream with that of the Listed Drugs in Module 1.14.3.1, and the approved labelling text for Listed Drugs in Module 1.14.3.2?

FDA Response to Question 1:
Your proposal to provide an annotated comparison of labeling for MC2-01 cream with that of the Listed Drugs appears reasonable.

Question 2:
Does the Agency agree that the content of Module 2 to 5 provides a complete application and support a substantial review of the 505(b)(2) application?

FDA Response to Question 2:
We have the following comments regarding the proposed table of contents (TOC: Table 24-27, page 78):

- (b) (4)

- Your TOC does not appear to include Module 2. In Module 2, you need to provide a comprehensive review of the efficacy, safety and pharmacology data from your development program to support the approval of your product. The submission of individual final study reports in Module 5 is not sufficient. Topics to discuss in your Summary of Clinical Safety include:

    - Risk and benefit assessment of your product compared to other marketed products for the same indication.

    - Local safety findings across the trials in your development program as you conducted no provocative dermal safety assessments,

    - Applicability of foreign data to the United States population.

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

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1a: Drug Master Files
Does the Agency agree that the approach described for referencing Drug Master files is appropriate, and provides the required information for the drug substances for the NDA?

FDA Response to Question 1a:
It is acceptable to reference the API information in DMFs (b) (4) with an appropriate Letter of Authorization. However, in addition to information on incoming test and acceptance criteria for the drug substance and details on analytical methods and related validations, for ease of review, we also request the following information be provided to the NDA on each drug substance:

- General information
- Physico-chemical properties
- Certificate of Analysis of the drug substances used in the clinical trial.

Question 1b: Drug Master Files

Does the Agency agree that the approach described for referencing Drug Master files is appropriate, and provides the required information for the primary packaging materials for the NDA?

FDA Response to Question 1b:

Your approach to cross reference DMF is acceptable. Provide test results of the extractable/leachable studies for the container/closure components in the NDA submission.

Question 2: Test Methods Used in Drug Product Specifications

Does the agency agree that the tests outlined in the Drug Product Specifications appropriately ensure the quality of the commercial products?

FDA Response to Question 2:

Add tests for (b) (4) and elemental impurities at release, and weight loss during the stability studies, in the drug product specification or provide justification for why these tests are not needed.

Meeting Discussion:

The sponsor will submit their justification for whether the tests for (b) (4) and elemental impurities at release, and weight loss during the stability studies as per USP monograph in the NDA submission.

Question 3a: (b) (4)

(b) (4)

FDA Response to Question 3b:

(b) (4)

Question 4: Planned Change in (b) (4) for 60 g Tube Size

Does the Agency agree that inclusion of a comparability protocol in the NDA submission is an appropriate mechanism for facilitating a change in (b) (4) and that an appropriately designed compatibility protocol will allow for the change to be considered a minor change (and thus annually reportable)?

FDA Response to Question 4:

Your proposal to submit a comparability protocol in the NDA for a post approval (b) (4) change is acceptable. We will review and determine the adequacy of the comparability protocol during the NDA review. However, the proposed post-approval change (b) (4) is considered a moderate change and you should submit the data from comparability/compatibility testing (b) (4) in a CBE-30 post-approval supplement.

Question 5: Stability Package for MC2-01 Cream in Aluminum Tubes 60g Size

Does the Agency agree that the proposed drug product stability data package is adequate for NDA submission?

FDA Response to Question 5:

The proposed drug product stability package for the 60g size appears to be acceptable.

Question 6: Process Validation

Does the Agency expect to see an outline of the process validation protocol as part of the NDA?

FDA Response to Question 6:

We concur with your proposed plan.

Question 7a:

Does the agency agree that an overview of the method validation package presented in section 3.2.R.3.P with a reference to 3.2.P.5.3 is an appropriate approach?

FDA Response to Question 7a:

Your plans for analytical method validation package and drug product samples appear to be acceptable.

Question 7b: Analytical Method Validation Package and Trade Samples

Does the Agency find the plan acceptable not to include representative drug product trade samples part of the initial NDA?

FDA Response to Question 7b:
You do not have to submit representative trade samples at the time of the submission of your application. However, be advised that we will request that you submit representative trade samples from the exhibit batches of the drug product during the early part of the review cycle. Exhibit batches should be manufactured minimally at 1:10 of the commercial scale at the proposed commercial manufacturing site with the same process/equipment and packaged in the container closure intended for the commercial drug product.

2.3. Nonclinical

Question 1: SEND data
Does the Agency agree that tabulation datasets (SEND) is to be provided for the pivotal 90 days repeat-dose toxicity study only?

FDA Response to Question 1:
Yes, we agree.

Question 2: Data to be Submitted at Day 30
Does the Agency find it acceptable that the final audited report and the corresponding SEND data for the 90 days repeat toxicity study in minipigs are submitted within 30 calendar days of the original NDA submission?

FDA Response to Question 2:
Yes, it is acceptable to submit the final audited report for the 90-day dermal toxicity study in minipigs within 30 calendar days of the original NDA submission.

We note that the 90-day dermal toxicity study in minipigs was conducted with a 5-day treatment and 2-day non-treatment weekly dosing regimen. This is not the typical weekly dosing regimen used for topical drug products in repeat dose dermal toxicity studies (i.e., 7 days per week of treatment). Provide a detailed rationale for the selected dosing regimen used in this study in the original NDA submission. The adequacy of this study will be determined after review of the full study report.

Question 3: USPI – Presentation of Pregnancy Labeling and Lactation Section
Does the Agency agree with the approach prosed for USPI Section 8.1-8.3 Use in Special Populations?

FDA Response to Question 3:
Your proposed approach of not submitting a PLLR converted labeling for your topical drug product with the original NDA submission is not acceptable. The labeling for your topical drug product should conform with PLLR requirements regardless if the listed drug is currently in PLLR format or not.

Question 4: Nonclinical Package
Does the Agency agree that the 90-days repeat toxicity in minipigs completes the non-clinical data package for the NDA submission for MC2-01 cream?

FDA Response to Question 4:
The 90-day dermal repeat dose toxicity study in minipigs may complete the nonclinical data package for your NDA submission. However, the adequacy of the data will be a review issue under the NDA. Refer to the Agency response for Question 2 for concerns associated with the conduct of the 90-day dermal repeat dose toxicity study in minipigs.

Question 5: Nonclinical Published Literature
Does the Agency agree?

FDA Response to Question 5:
Yes, we agree that if needed, literature references can be provided upon request.

2.4. Clinical/Biostatistics/ Clinical Pharmacology

Question 1: Clinical Package
Does the Agency agree that the proposed clinical package support the NDA submission, and that no additional clinical studies are required for the filing of the MC2-01 cream US marketing application?

FDA Response to Question 1:
We acknowledge that you submitted “waiver requests” for the evaluation of phototoxicity, photoallergenicity and the proarrhythmic potential of your proposed product (SD 40 dated 1/15/2019; SD 35 dated 12/12/2018). Your requests to not conduct these studies are under review. The outcome of our review will inform our decision regarding whether additional studies are needed.

Question 2: Pooling of Local Safety and Tolerability
Given the difference in the design of the pivotal phase 3 (MC2-01-C2) and the MUsT (MC2-01-C3), does the Agency agree that pooling of safety and tolerability data from the two trials may not be meaningful?

FDA Response to Question 2:
We agree.

Question 3: Integrated Summary of Efficacy and Integrated Summary of Safety
Does the Agency agree that an ISE and ISS is not required the NDA application?

FDA Response to Question 3:
We agree. In the absence of pooled data, provide your detailed safety and efficacy summaries and risk benefit discussion in Module 2 (Section 2.7.4 and 2.7.5).

Question 4: Subject Narrative and Case Report Forms
Does the Agency agree with this proposal regarding Subject narrative and Case Report forms?

FDA Response to Question 4:
For your Phase 2 and Phase 3 trials, you propose to provide subject narratives and Case Report Forms (CRFs) for all deaths, serious adverse events (SAEs), and adverse events resulting in discontinuation of treatment. In addition, provide narratives for all pregnancies, subjects who experienced hypersensitivity reactions and adverse events of special interest (adverse events related to calcium metabolism or HPA axis suppression.) If the CRFs and narratives are located in the Clinical Study Reports (CSR), then provide links to this information in the relevant sections of the Overview of Clinical Safety and Summary of Clinical Safety.

Question 5: Datasets for Phase 2 (MC2-01-03) and Phase 3 (MC2-01-C2)
Does the Agency agree with this proposal regarding analysis datasets?

FDA Response to Question 5:
We agree with your proposal to submit Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets for the Phase 2 trial (MC2-01-C3) and the Phase 3 trial (MC2-01-C2).

The primary method for handling missing efficacy data in your Phase 3 trial is the Multiple Imputation (MI) approach, which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets. The SAS code should be self-contained and executable with the datasets submitted in the NDA.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code

used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

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

From technical standpoint, your proposed dataset plan for Phase 2 trial (MC2-01-C3) and Phase 3 trial (MC2-01-C2) is acceptable; however, for other studies, CDISC standards are required if the study starts after December 17, 2016 and data are submitted in module 5, sections 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.2, 5.3.3.3, 5.3.3.4, 5.3.4, 5.3.5.1, 5.3.5.2.

Question 6: Annotated Case Report Forms for Phase 2 (MC2-01-C3) and Phase 3 (MC2-01-C2)

Does the Agency agree with the proposal for sample annotated case report forms?

FDA Response to Question 6:
Yes, we agree.

Question 7: Subject-Level Data Line Listings by Clinical Site and Summary-Level Clinical Site Dataset

Does the Agency agree that submission of datasets for the pivotal Phase 3 MC2-01-C2 clinical trial fulfils the requirements as provided in the Bioresearch Monitoring Technical Conformance Guide?

FDA Response to Question 7:
Yes. Submit Bioresearch Monitoring (BIMO) datasets only for those studies considered to be pivotal by the review division.

Question 8: Four Month (120 days) Safety Update
Does the Agency agree with the proposed scope (contents and data cut-off) of the 4-month Safety Update?

FDA Response to Question 8:
Per 21 CFR 314.50, the safety update report (SUR), needs to update the New Drug Application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. SUR must include the same kinds of summary information in the same format as the original submission. See additional comments. Ensure that you provide narratives and CRFs in the SUR for all subjects who died, experienced SAEs, hypersensitivity reactions, pregnancy, discontinued the trial due to an AE and reported

an AEs of special interest related to calcium metabolism or systemic effects of corticosteroids.

We agree with the proposed content (summary safety information from Trials MC2-01-C6 and MC2-01-C7) and data cut-off (90 days) for the SUR.

Question 9: Financial Disclosures (FDA Form 3454 and FDA Form 3455)
Does the Agency agree that the submission of financial certification and disclosure statements for the pivotal Phase 3 (MC2-01-C2) and for the MUsT (MC2-01-C3 fulfils the requirements laid out in 21 CFR Part 54?

FDA Response to Question 9:
Yes, we agree.

Question 10: Risk Evaluation and Mitigation Strategy (REMS)
Does the Agency agree that a REMS is not required for MC@-01 cream?

FDA Response to Question 10:
In view of the available safety information regarding calcipotriene and betamethasone, product labeling may be sufficient to ensure the safe use of your product in the treatment of plaque psoriasis. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the NDA review.

(b) (4)

(b) (4)

Question 12: Clinical Published Literature
Does the Agency agree?

FDA Response to Question 12:
Application needs to be substantially complete at the time of submission. All literature that is necessary to support approval of your product needs to be provided in the submission. Refer to the Administrative Comments regarding 505(b)(2).

Additional Comments

Provide the following in your analysis of the Phase 3 trial data:

- 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.
- 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.
- Safety analyses in subgroups of subjects by sex, race, age group (< 18 years and ≥ 18 years; < 65 years and ≥ 65 years), ethnicity and baseline severity.
- Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug.
- 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, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

In your NDA submission we recommend you include the following.

1. Bioanalytical method validation and bioanalysis reports of all the active moieties and metabolites as well as serum and urine calcium and serum cortisol.

2. In a tabulated form, provide a summary of the bioanalytical method validation parameters of all the analytes mentioned above and also include information to support sample storage stability to cover the duration from sample collection in the clinic to the time of bioanalysis.

3. Provide all pharmacokinetic (PK) data in SAS transport format for review.

3.0 Administrative Comments

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations.

See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2))

and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.
In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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.

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.”

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/

KENDALL A MARCUS
08/14/2019 01:49:46 PM