CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209355Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 126779

MEETING PRELIMINARY COMMENTS

Dow Pharmaceutical Sciences, Inc.
c/o Valeant Pharmaceuticals North America, LLC
Attention: Sean Humphrey
Senior Manager, Regulatory Affairs
1330 Redwood Way, Suite C
Petaluma, CA 94954

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 halobetasol propionate lotion.

We also refer to your June 8, 2017, correspondence, received June 8, 2017, requesting a meeting to discuss the development program for halobetasol propionate lotion.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Barbara Gould, MBAHCM
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 2, 2017, 11:00 a.m. – 12:00 p.m. EST
Meeting Location: Teleconference

Application Number: IND 126779
Product Name: halobetasol propionate lotion
Proposed Indication: Treatment of (b) (4) plaque psoriasis in patients 18 years of age and older
Sponsor Name: Dow Pharmaceutical Sciences, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for August 2, 2017 at 11:00 a.m. between Dow Pharmaceutical Sciences, Inc. and the Division of Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Purpose of Teleconference:
The purpose of this teleconference is to discuss the development program for halobetasol propionate lotion.

Regulatory Correspondence History:

We have sent the following correspondences:

- 6/13/2016 iPSP – initial agreement
- 5/2/2016 iPSP – written response
- 10/2/2015 Study may proceed letter

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls (CMC)

Question 1:

DPS is proposing specifications in accordance with current International Council for Harmonisation (ICH) Q6A for drug substance and drug product. Halobetasol propionate drug substance is described in a United States Pharmacopeia (USP) monograph. The proposed specifications are comprehensive and based on current ICH guidelines. Details of the proposed specifications are included in Appendix 1.6.2.13.4. We acknowledge that the suitability of the acceptance criteria could be an NDA review issue and are subject to change based on final stability data to be presented in the NDA.

a. *Based on the specifications provided in the briefing book, does the Agency have any recommendations for the drug substance specifications proposed for halobetasol propionate?*

b. *Based on the specifications provided in the briefing book, does the Agency have any recommendations for the drug product specifications proposed for use in commercial drug product?*

FDA Response to Question 1:

From the drug substance standpoint, your proposal to cross-reference a DMF with the appropriate Letter of Authorization is reasonable. Adherence to USP standards is reasonable as well. However, if the manufacturing process for the API generates impurities that are not included in the USP monograph specifications, these additional impurities should also be included in the specification and reported.

The tests included in the drug product specification appear reasonable. The test methods and acceptance criteria of the drug product specification will be evaluated during NDA review.

Question 2:

For other topical marketed products, the physician's sample size has not been tested routinely per USP<3> uniformity in containers. Given that the maximum daily dose is 7 g/day, the physician sample size of 3 g can be considered for one time use only, and thus, exempt from testing the USP <3> uniformity in containers.

Does the Agency agree that the 3 g physician sample size is exempt from testing the USP<3> uniformity in containers?

FDA Response to Question 2:
Your proposal of not conducting uniformity in containers test on the 3 g physician samples appears reasonable.

Question 3:
Dow Pharmaceutical Sciences has conducted ICH registration stability studies in accordance with ICH Q1A guideline using a (b) (4) batch size. The bracketing design for the ICH stability batches, a sample (3-g fill size) and 3 trade sizes (45-g, 60-g, and 100-g fill sizes), was previously proposed and accepted as per the EOP2 Meeting held on 03 June 2015 (meeting minutes are in Appendix 1.6.2.13.3).

For the process validation batches (also made at the (b) (4) batch size), the bracketing design will include the 3, 60 and 100 g fill sizes only. The process validation lots and the routine commercial batches will be tested at the long-term condition in the horizontal orientation only. The details of the stability studies and package for the tube fill sizes will be provided in the briefing book.

The details of the stability studies and package types for the tube fill sizes are provided in Appendix 1.6.2.13.4.

a. *Does the Agency agree that the stability program described in the briefing document for the ICH (registration) stability batches adequately meets the filing requirements for the NDA?*

b. *Does the Agency agree that the stability programs described in the briefing document for the process validation and routine commercial stability lots are acceptable?*

c. *Does the Agency agree that the additional stability studies (i.e. photostability, temperature cycling (both freeze/thaw and cold/warm), in-use testing) and leachable/extractables assessment will adequately support filing and registration?*

FDA Response to Question 3:

a. Yes. The stability program described in the briefing document for the ICH (registration) stability batches appears reasonable to support your NDA filing.

b. Yes. The stability programs described in the briefing document for the process validation and routine commercial stability lots appear reasonable to ensure the product quality.

c. Yes. The additional stability studies (i.e. photostability, temperature cycling, in-use testing) and leachable/extractables assessment appear reasonable to support your NDA filing. **Note:** The in-use stability study should be conducted on aged stability samples taken from the long-term stability study at representative testing time points.

2.2. Nonclinical

Question 4:

The IDP-122 Lotion nonclinical development program was discussed and agreed upon with the Agency at the EOP2 meeting. The Sponsor assessed the local and systemic toxicity of IDP-122 Lotion in a 3-month repeat dose dermal minipig toxicity, and local tolerance in skin sensitization and ocular irritation studies. The Sponsor intends to reference ULTRAVATE Cream (0.05%) drug product label for genotoxicity, carcinogenicity and reproductive and developmental toxicity information.

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-122 Lotion?

FDA Response to Question 4:
Yes, we agree if you are able to generate adequate clinical bridge to the listed drug.

2.3. Clinical

Question 5:
Based on the completion of the clinical program as detailed in Section 1.6.2.7.4, does the Agency agree that the clinical program is adequate to support approval of IDP-122 Lotion with an indication for the topical treatment of psoriasis?

FDA Response to Question 5:

The clinical development plan for IDP-122 Lotion includes the following eight studies:

- a Phase 1 potency-ranking study (V01-118A-101)
- a Phase 1, 21-day cumulative irritation study (V01-118A-102)
- a Phase 1 repeat insult patch test (RIPT) study (V01-118A-103)
- a Phase 1 maximal use PK and bridging study between IDP-122 Lotion and ULTRAVATE Cream, 0.05% (V01-118A-501)
- a Phase 2 safety and efficacy study comparing IDP-118 Lotion with its monads (i.e., IDP-122 Lotion, tazarotene 0.045% lotion, and vehicle; the IDP-118 Lotion vehicle evaluated in this study was identical to the IDP-122 Lotion vehicle) (V01-118A-201)
- a Phase 2 bridging study between IDP-122 Lotion and ULTRAVATE Cream, 0.05% (V01-122A-203)
- two Phase 3 safety and efficacy between IDP-122 Lotion and IDP-122 Lotion vehicle (V01-122A-301 and V01-122A-302)

Note: Per the EOP2 meeting (meeting date June 3, 2015):

1. The Agency granted a waiver for conduct of clinical photosafety studies.
2. The Agency stated that a waiver for conducting a long term safety study for IDP-122 would be acceptable, if the sponsor constructed an adequate clinical bridge to ULTRAVATE cream, 0.05%.

The clinical program appears to be adequate to support a marketing application. Approvability is a review issue.

Question 6:

A total of approximately 730 human subjects will have been exposed to at least 1 dose of IDP-122 Lotion and will be included in the NDA submission as part of the safety database. Of these, approximately 425 are subjects with psoriasis and treated with the to-be-marketed formulation of IDP-122 Lotion.

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

FDA Response to Question 6:

Of the 425 subjects with psoriasis who were treated with the to-be-marketed formulation of IDP-122 Lotion, approximately 365 were treated for at least 8 weeks (the intended dosing duration for the to-be-marketed product). See FDA Response to Question 5 regarding a waiver for conducting a long term safety study with IDP-122 lotion.

The total subject exposure appears to be adequate to support a marketing application. Approvability is a review issue.

Question 7:

The Sponsor plans to provide Bioresearch Monitoring (BIMO) Clinical Data in the electronic common technical document (eCTD) format. For each pivotal Phase 3 study, the following will be provided in Module 5, Section 5.3.5.4:

- BIMO 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 site 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 site (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 7:
Yes, we agree with the eCTD location of the BIMO information. Refer to the "Office of Scientific Investigations (OSI) Requests" at the end of this document for more information.

Question 8:
In the EOP2 meeting minutes dated 22 June 2015 the Agency stated that a QT/QTc waiver would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure of HP following IDP-122 Lotion treatment under maximal use conditions is low and less than or similar to those following treatment with the LD.

Based on topline PK data, drug bioavailability has been shown to be low and similar to that of ULTRAVATE Cream 0.05%.

Does the Agency agree that a waiver to conduct a thorough QT study to assess the potential of QT prolongation with the use of IDP-122 Lotion appears reasonable?

FDA Response to Question 8:
The comparable systemic exposure to HP observed after treatment with Ultravate cream and IDP-122 lotion under maximal usage conditions may support a request for a waiver of a thorough QT study.

Question 9:
For the 2 pivotal Phase 3 studies (V01-122A-301 and V01-122A-301) the Sponsor plans to submit case report forms in Appendix 16.3 by site 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)
- Discontinued due to an AEs 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 9:
This is acceptable. Additional case report forms may be requested during the review cycle.

Provide narratives for all subjects in the above-referenced categories. Include the corresponding study day of relevant events in the subject narratives e.g., "The adverse event occurred on xx/yy/2017 (Study Day zz)…"

Include reference ranges for laboratory values in the data listings where those laboratory values are presented and "flag" all laboratory values and vital signs that are outside of the reference ranges.

2.4. Statistics

Question 10:
The complete list of clinical studies is presented in Table 7. The datasets for the following clinical studies will be included in the NDA in CDISC format:

- V01-122A-301 (Phase 3 safety and efficacy)
- V01-122A-302 (Phase 3 safety and efficacy)
- V01-118A-201 (Phase 2 safety and efficacy)
- V01-122A-203 (Phase 2 safety and efficacy bridge to ULTRAVATE Cream)
- V01-118A-501 (Phase 1 maximal use PK bridge to ULTRAVATE Cream)
- V01-118A-102 (21-day cumulative irritation)
- V01-118A-103 (RIPT)

The datasets for all other IND studies (V01-118A-101 [potency study]) will be included in the NDA as SAS transport files.

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

FDA Response to Question 10:
Your proposal to submit datasets according to CDISC formatting is acceptable.

The primary method for handling missing efficacy data in your Phase 3 trials 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.

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

- Each efficacy 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. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- 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, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 11:
Statistical analysis of the safety data for the Phase 3 studies V01-122A-301 and V01-122A-302 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Safety (ISS). A copy of the ISS statistical analysis plan is included in Appendix 1.6.2.13.5. 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 11:
The statistical analysis plan for the integrated summary of safety (ISS) appears reasonable.

Your proposal to provide the ISS text document in Module 2, Section 2.7.4 and datasets in Module 5, Section 5.3.5.1 is acceptable.

Consider including safety data from the relevant arms of the Phase 2 study, V01-118A-201 in the pooled safety analyses. Also, provide your plans for 120-Day safety update.

Question 12:
Statistical analysis of the efficacy data for the Phase 3 studies V01-122A-301 and V01-122A-302 conducted with the to-be-marketed formulation will be pooled and presented in the Integrated Summary of Efficacy (ISE). A copy of the ISE statistical analysis plan is included in the Appendix 1.6.2.13.6. 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 12:

The statistical analysis plan for the integrated summary of efficacy (ISE) appears reasonable.

Your proposal to provide the ISE text document in Module 2, Section 2.7.3 and datasets in Module 5, Section 5.3.5.1 is acceptable.

2.5. Regulatory

Question 13:
The Sponsor proposes to submit the IDP-122 Lotion NDA in eCTD format with a complete XML backbone. The proposed content for Modules 1-5 is provided in Appendix 1.6.2.13.7.

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

FDA Response to Question 13:
From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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

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

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

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

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

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

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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

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

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

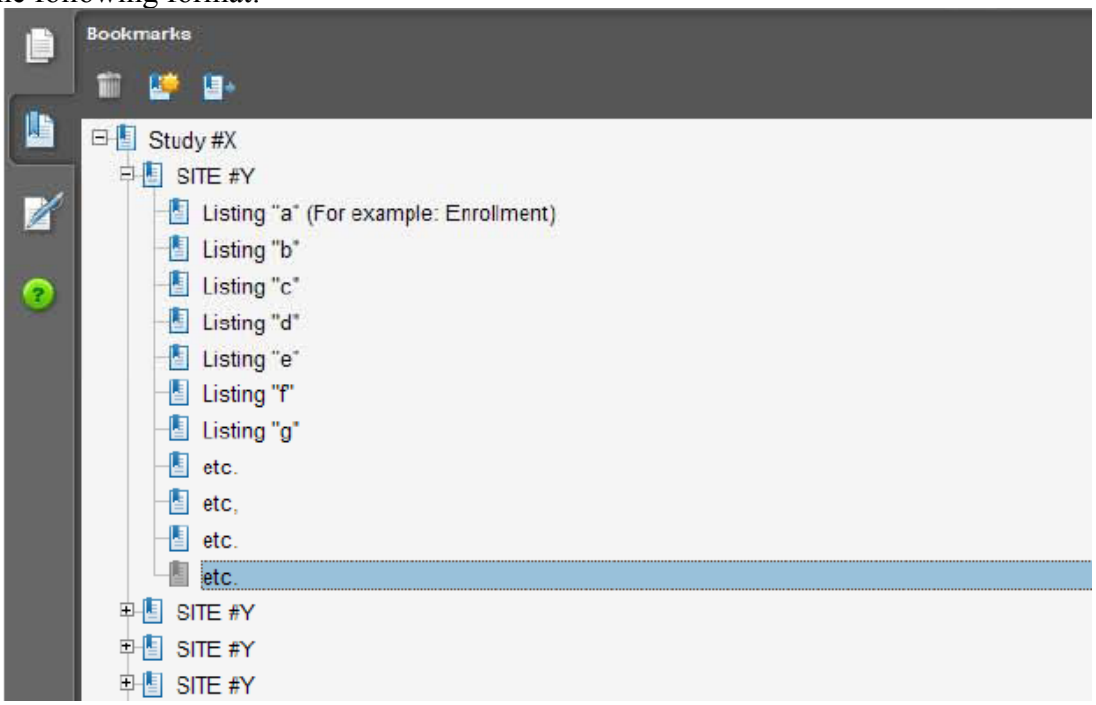
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records,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

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

II. Request for Subject Level Data Listings by Site

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

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



III. Request for Site Level Dataset:

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

641 **Attachment 1**

642 **Technical Instructions:**
643 **Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**
644
645
646 A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in
647 the chart below, the files should be linked into the Study Tagging File (STF) for each
648 study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief
649 description of file being submitted]." In addition, a BIMO STF should be constructed
650 and placed in Module 5.3.5.4, Other Study reports and related information. The study ID
651 for this STF should be "bimo." Files for items I, II and III below should be linked into
652 this BIMO STF, using file tags indicated below. The item III site-level dataset filename
653 should be "clinsite.xpt."
654

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

655
656 B. In addition, within the directory structure, the item III site-level dataset should be placed
657 in the M5 folder as follows:
658

659
660
661 C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included.
662 If this Guide is included, it should be included in the BIMO STF. The leaf title should be
663 "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements
664 being submitted with hyperlinks to those elements in Module 5.
665

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

References:

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

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

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

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

/s/

BARBARA J GOULD
07/26/2017