

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211882Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 126277

MEETING PRELIMINARY COMMENTS

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

Dear Mr. Humphries:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tazarotene lotion, 0.045%.

We also refer to your October 11, 2018, correspondence, received October 11, 2018, requesting a meeting to discuss the overall organization for submission of New Drug Application (NDA).

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: PNDA

Meeting Date and Time: November 13, 2018 at 2:05 PM
Meeting Location: Teleconference

Application Number: IND 126277
Product Name: tazarotene lotion, 0.045%

Proposed Indication: For the topical treatment of acne vulgaris in patients 9 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 October 25, 2018 at between Dow Pharmaceutical Sciences, Inc. and the Division of Dermatology and Dental Product. 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. 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). Contact the Regulatory Project Manager (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

The purpose of this PNDA meeting is to discuss the format and content for future marketing application to support the proposed indication of acne vulgaris in patients 9 years of age and older.

2.0 DISCUSSION

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 12/06/2016 End of Phase 2 Meeting

We have sent the following correspondences:

- 08/09/2017 Advice Letter
- 08/02/2017 Pediatric Study Plan – Written Response
- 10/20/2015 Study May Proceed

2.1. Regulatory

Introductory Comment:

If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., reliance on the FDA’s finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.

You are proposing to reference information from the Summary Basis of Approval (SBA) and FDA reviewers’ public summaries for support of the safety of your product. “Full reports of investigations” of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. The SBA and FDA reviewers’ public summaries, however, do not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency’s finding of safety and/or effectiveness for a listed drug may rely on FDA’s finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug.

Within your background package you make reference to (b) (4). Clarify if you intend to rely on our finding of safety for each of those listed drugs to support your marketing application. 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.

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.

You 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)).

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Question 19:

The Sponsor intends to request a partial waiver for the conduct of clinical studies with IDP-123 Lotion in pediatric subjects aged 0 to 8 years 11 months due to the very low prevalence of acne in this age group. The Sponsor included subjects 9 years of age and above in clinical studies with IDP-123 Lotion. The agreed to iPSP was submitted to IND 126277 on 15 August 2017 (Sequence 0017).

Does the Agency agree with the Sponsor's request for partial waiver for pediatric subjects aged 0 to 8 years 11 months?

FDA Response to Question 19:

Your iPSP is currently pending internal consultation with the Pediatric Research Equity Committee (PeRC) with a target date to provide you with final decision by November 22, 2018.

Question 20:

The Sponsor proposes to submit the IDP-123 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 package?

FDA Response to Question 20:

Your proposal appears reasonable.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1:

DPS is proposing specifications in accordance with the current International Council for Harmonisation (ICH) guideline Q6A for drug substance and drug product. Tazarotene drug substance is described in the manufacturer's drug master file (b) (4). Details of the proposed specifications are provided in the briefing package (Section 1.6.2.13.1). 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 package, does the Agency have any recommendations for the drug substance specifications proposed for tazarotene?*
- b. *Based on the specifications provided in the briefing package, does the Agency have any recommendations for the drug product specifications proposed for use in commercial drug product?*

FDA Response to Question 1:

- a. The proposed drug substance specifications appear reasonable. In addition to the drug substance specifications submitted, you should evaluate the need to control the polymorphic form, particle size distribution and the elemental impurities of the drug

substance in the specifications. Since you have made reference to DMF (b) (4), refer to FDA DMF related comments dated on 02 December 2016.

- b. The submitted drug product specifications appear reasonable. However, emulsion droplet size should be tested at release as well as on stability. See further comments under the FDA Response to Q3.

We may have further comments for the test and acceptance criteria in the specifications for both drug substance and drug product based on the totality of the overall data during NDA review.

Question 2:

For other topical marketed products, the physician's sample size has not been tested routinely per United States Pharmacopeia (USP) <3> uniformity in containers. Given that the maximum daily dose is approximately (b) (4) g/day, the physician sample size of 3 g can be considered for 1 time use only, and thus, exempt from testing by USP <3> uniformity in containers.

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

FDA Response to Question 2:

We agree. However, the content uniformity is one of the critical quality attributes of the lotion dosage form. Even though 3-g physician sample is a single dose unit, we still recommend you test the container content uniformity per USP <905>. The final recommendation will be made based on the totality of the data submitted at the time of NDA review.

Question 3:

DPS has evaluated emulsion droplet size for 9 bulk commercial scale batches (b) (4) filled in various packaging configurations for (b) (4) and IDP-123 for a total of (b) (4) packaged lots. As these drug products contain the same Vehicle Lotion as described above, the D10, D50, and D90 results are consistent across storage conditions, time points and packaging configurations. It is proposed that the emulsion droplet specification be tested (b) (4)

Does the Agency agree that these studies support testing of this attribute for (b) (4) (b) (4)?

FDA Response to Question 3:

No, we do not agree.

(b) (4)
(b) (4)
(b) (4)
specification should be tested for the proposed drug product at release as well as on stability. If this NDA is approved for marketing, we recommend you submit a post-approval supplement to

request removal of this test once adequate commercial scale batch stability data has been generated with this specific formulation to justify the elimination of this test during shelf life.

Question 4:

DPS has conducted ICH registration stability studies in accordance with ICH Q1A guideline using a (b) (4) kg batch size. The 3 ICH stability batches consisted of a sample (3-g fill size) and trade size (45-g fill size) stored at long term, intermediate and accelerated conditions in the inverted and horizontal orientation. This design was accepted as per the EOP2 Meeting request submitted on 14 October 2016 (IND 126277, sequence 0010) and in the FDA meeting preliminary feedback dated 02 December 2016.

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 are provided in Section 1.6.2.13.1.

- a. Does the Agency agree that the stability program described in the briefing package 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 package for the process validation and routine commercial stability lots are acceptable?

FDA Response to Question 4:

Your stability program including the process validation and routine commercial lots appears reasonable to support the NDA submission. You should also refer to FDA End of Phase 2 preliminary comments for CMC question Q2 dated December 2, 2018.

Final recommendation regarding the drug product stability testing will be made during NDA reviews based on the totality of the submitted data.

Question 5:

In addition to the ICH stability studies, DPS conducted the following studies: photostability, temperature cycling (both freeze/thaw and cold/warm), in-use testing and leachables/extractables assessment in the proposed commercial container closure. A brief description of these studies is provided in Section 1.6.2.13.1. The results of these studies will be summarized in Sections 3.2.P.2.4, Container Closure System, and 3.2.P.8.1, Stability Summary and Conclusion, of the NDA.

Does the Agency concur that these studies will adequately support filing and registration?

FDA Response to Question 5:

Your stability program appears reasonable to support the NDA submission. We may have further comments during NDA review based on the totality of data.

2.3. Pharmacology/Toxicology

Question 6:

The IDP-123 Lotion nonclinical development program was discussed and agreed upon with the Agency at the EOP2 meeting. For the drug product, IDP-123 Lotion, DPS intends to provide repeated dose toxicity and local tolerance data. Additionally, the Sponsor intends to rely on the Agency's prior findings of safety for the LD, Tazorac Cream 0.1% (NDA 021184), specifically genotoxicity, reproductive toxicity, and carcinogenicity data.

The results of the Phase 1 PK bridging study (V01-123A-501) used for relative bioavailability assessment suggest that the systemic exposure of IDP-123 Lotion (all ages combined) is similar to the LD.

- a. Does the Agency agree that the Sponsor's assessment of comparative bioavailability from the PK bridging study data is sufficient to establish an adequate clinical bridge to the LD?
- 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-123 Lotion and that no additional toxicity studies will be required?

FDA Response to Question 6:

- a. Refer to FDA responses for Questions 7 and 17.
- b. Yes, we agree that no additional nonclinical studies would be required to support a 505(b)(2) NDA for IDP-123 Lotion if it is determined that you have established an adequate clinical bridge to the listed drug.

2.4. Clinical Pharmacology

Question 17:

In order to establish comparative bioavailability, the Sponsor compared IDP-123 Lotion with Tazorac Cream (LD) exposure in subjects aged 12 and above as part of the maximum use clinical PK study (V01-123A-501). Relative bioavailability assessment was conducted by calculating the ratio of the geometric means and the corresponding 90% CI for tazarotene C_{max} and AUC from IDP-123 Lotion over those for Tazorac Cream; geometric mean ratios and corresponding 90% CIs were similarly calculated for tazarotenic acid C_{max} and AUC. The results of this analysis, as presented in the briefing package, demonstrate comparable bioavailability for IDP-123 Lotion versus the LD.

Does the Agency agree that the data presented provide evidence of comparative bioavailability between IDP-123 Lotion and Tazorac Cream?

FDA Response to Question 17:

The results from the study V01-123A-501 appear to demonstrate that the systemic exposures of tazarotene and tazarotenic acid following application of IDP-123 Lotion are similar or less compared to the exposures following application of Tazorac cream in subjects aged 12 and

above. The final determination will be made at the time of NDA submission following detailed review of your study report and associated bioanalytical method validation and bioanalysis reports.

Question 18:

The PK profile for IDP-123 Lotion has been established in subjects 9 years of age and older (V01-123A-501). Systemic exposure in subjects aged 9 to < 12 years of age were found to be higher than for subjects aged $\geq$ 12 years of age. The adverse event profiles in these two age groups were similar. Furthermore, there are adequate exposure safety margins to nonclinical toxicity studies in subjects 9 to < 12 years of age. Additionally, the safety of IDP-123 Lotion in ages 9 and above was established in the two Phase 3 studies.

Does the Agency agree that the available data, as summarized in this briefing package, supports the safety of IDP-123 Lotion at the observed maximal use PK exposures in the target population of 9 years of age and older?

FDA Response to Question 18:

It is premature to agree whether the available data would support the safety of IDP-123 Lotion in the target population down to 9 years of age without reviewing your study reports and associated bioanalytical method validation and bioanalysis reports. This determination will be made during the review of your NDA submission.

In your NDA submission, provide a justification to support higher systemic exposure of IDP-123 Lotion in subjects 9 to <12 years of age compared to subjects 12 years of age and older.

2.5. Clinical/Biostatistics

Question 7:

The bridging strategy to Tazorac Cream 0.1% was agreed upon with the FDA at the pre-IND meeting held 17 June 2015 and again at the EOP2 meeting. The program includes a PK bridging study, V01-123A-501, and a safety and efficacy bridging study, V01-123A-201. The results from these studies, as summarized in this briefing package, suggest an adequate clinical bridge has been established.

Does the Agency agree that the results from the bridging studies are adequate to establish a clinical bridge to Tazorac Cream 0.1% and allow for a successful 505(b)(2) NDA pathway for IDP-123 Lotion?

FDA Response to Question 7:

Yes, pending review of the final study reports under the NDA.

Question 8:

Based on the completion of the clinical program as detailed in the briefing package, does the Agency agree that the clinical program is adequate to support approval of IDP-123 Lotion with an indication for the topical treatment of acne?

FDA Response to Question 8:

The clinical program appears adequate for filing and review under the NDA. Determination of specific labeling will be discussed during the second half of the NDA review.

Question 9:

A total of approximately 1174 human subjects will have been exposed to at least 1 dose of IDP-123 Lotion and will be included in the NDA submission as part of the safety database. Of these, approximately 897 are subjects with acne and treated with the to-be-marketed formulation of IDP-123 Lotion.

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

FDA Response to Question 9:

Yes, unless some new safety issue is identified following review of the clinical study reports.

Question 10:

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 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 10:

Yes, we agree with the location and the approach appears acceptable. Please refer to the February 2018 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. When final, this guidance will represent FDA’s current thinking on the topic. The guidance is available at the following link:
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332466.pdf>

Question 11:

For the 2 pivotal Phase 3 studies (V01-123A-301 and V01-123A-302) the Sponsor plans to submit case report forms in Appendix 16.3 of the CSR 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 11:

With your NDA, submit electronic case report forms (eCRFs) for deaths, SAEs, AEs leading to discontinuations and withdrawals, and adverse events of special interest. eCRFs for subjects who were exposed to investigational product should be available upon request and for inspection during the review period. For the principal record keeping requirements for clinical investigators and sponsors developing drugs, see *Guidance for Industry, Electronic Source Data in Clinical Investigations*.

Question 12:

At the pre-IND meeting held 17 June 2015 and EOP2 meeting, 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 and the PK results from the Phase 1 PK bridging study provide evidence that the safety profile and systemic exposure of IDP-123 Lotion is similar for all ages combined to Tazorac Cream 0.1% and, consequently, would not require a separate long term safety study to support registration of IDP-123 Lotion.

Does the Agency agree that, based upon the available data, an adequate clinical bridge will be established and an additional long term safety study with IDP-123 Lotion is not needed for a 505(b)(2) NDA approval?

FDA Response to Question 12:

A long-term safety study does not appear necessary unless a new safety issue is identified following review of the clinical study reports.

Question 13:

Tazarotene formulated in Tazorac Cream and Gel, 0.05% and 0.1%, has been approved and commercialized for use since June 1997 (Tazorac Gel) with no associated reported cardiac events of interest (eg, torsades de pointes and cardiac arrhythmia).

In the pre-IND meeting minutes and EOP2 meeting (Section 1.6.2.13.2), the FDA stated a TQT waiver is reasonable, provided that the systemic exposure from IDP-123 Lotion is similar to the systemic exposure from Tazorac Cream 0.1%. The similar bioavailability of IDP-123 Lotion to Tazorac Cream 0.1%, based on the PK results from the Phase 1 bridging study, coupled with the lack of association between postmarketing tazarotene use and cardiac arrhythmias/adverse effects, indicate that a pro-arrhythmia risk is not anticipated with the use of IDP-123 Lotion. In addition, nonclinical data including in vitro hERG and ECGs in minipigs did not reveal any safety concerns. Therefore, DPS intends to request a waiver for conducting a clinical study with IDP-123 Lotion 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-123 Lotion is not needed for NDA filing and approval?

FDA Response to Question 13:

Yes.

Question 14:

The complete list of clinical studies is presented in Table 9. The datasets for the following clinical studies will be included in the NDA in CDISC format:

- V01-123A-301 (Phase 3 safety and efficacy)
- V01-123A-302 (Phase 3 safety and efficacy)
- V01-123A-201 (Phase 2 safety and efficacy bridge to Tazorac Cream)
- V01-123A-501 (Phase 1 maximal use PK bridge to Tazorac Cream)
- V01-123A-101 (21-day cumulative irritation)
- V01-123A-102 (RIPT)

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

FDA Response to Question 14:

We agree that the datasets for your clinical studies should be submitted in CDISC format. We recommend submitting the raw data in SDTM format and the analysis datasets in ADaM format. Submit the datasets in SAS transport format (.xpt). Ensure that the analysis datasets include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study reports.

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 dataset, algorithms for derived variables (including source variables used) and descriptions of the codes used in factor variables.

Because the protocols specified handling missing data using multiple imputation, clarify how you intend to submit the datasets. We recommend submitting the observed-case datasets along with complete statistical programs for conducting the multiple imputation through all stages of the analyses, so that the full analyses can be conducted from the observed-case datasets. Also include any additional statistical programs for non-standard or model-based analyses.

Include the study protocol, all protocol amendments, the statistical analysis plan, and an annotated copy of the case report form as well as the other required elements for the clinical trials.

Question 15:

Statistical analysis of the safety data for the Phase 3 studies V01-123A-301 and V01-123A-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 1.6.2.13.4. 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 15:

- a. Your proposal to provide descriptive safety summaries for the pooled Phase 3 studies appears reasonable.
- b. If you meet the size and complexity parameters described under ‘Option D’ of the guidance, then it is acceptable to include the narrative portion of the ISS in Section 2.7.4 and the appendices and datasets in Module 5. Note, however, that the appendices and datasets for the ISS should be included in Section 5.3.5.3 rather than 5.3.5.1.

Question 16:

Statistical analysis of the efficacy data for the Phase 3 studies V01-123A-301 and V01-123A-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 1.6.2.13.3. 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 16:

- a. Your proposal to provide descriptive efficacy summaries for the pooled Phase 3 studies appears reasonable. Refer also to the Guidance for Industry: *Integrated Summary of Effectiveness* for information on content and format of the ISE.
- b. If you meet the size and complexity parameters described under ‘Option D’ of the guidance, then it is acceptable to include the narrative portion of the ISE in Section 2.7.3 and the appendices and datasets in Module 5. Note, however, that the appendices and datasets for the ISE should be included in Section 5.3.5.3 rather than 5.3.5.1.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and effectiveness for a listed drug or by reliance on published literature

Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication A
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section B
4.	

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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

741 [https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequire](https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf)
742 [ments/UCM332468.pdf](https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf).
743
744

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/

BARBARA J GOULD
11/08/2018



IND 126277

MEETING PRELIMINARY COMMENTS

Dow Pharmaceuticals 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 tazarotene lotion, 0.045%.

We also refer to your October 14, 2016 correspondence, received October 14, 2016, requesting a meeting to discuss the development program for tazarotene lotion, 0.045%.

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 (240) 402-3842.

Sincerely,

{See appended electronic signature page}

Omolarai Laiyemo, PharmD
Regulatory Health Project Manager
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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: December 6, 2016 at 11:00 a.m. ET
Meeting Format: Teleconference

Application Number: IND 126277
Product Name: Tazarotene lotion, 0.045%.
Proposed Indication: Treatment of acne vulgaris
Sponsor Name: Dow Pharmaceuticals Sciences, Inc.

1 Introduction:

2 This material consists of our preliminary responses to your questions and any additional
3 comments in preparation for the discussion at the meeting scheduled for December 6, 2016
4 at 11:00 a.m. ET between Dow Pharmaceuticals Sciences, Inc. and the Division of
5 Dermatology and Dental Products. We are sharing this material to promote a collaborative
6 and successful discussion at the meeting. The meeting minutes will reflect agreements,
7 important issues, and any action items discussed during the meeting and may not be
8 identical to these preliminary comments following substantive discussion at the meeting.
9 However, if these answers and comments are clear to you and you determine that further
10 discussion is not required, you have the option of cancelling the meeting (contact the
11 regulatory project manager (RPM)). If you choose to cancel the meeting, this document
12 will represent the official record of the meeting. If you determine that discussion is needed
13 for only some of the original questions, you have the option of reducing the agenda. It is
14 important to remember that some meetings, particularly milestone meetings, can be
15 valuable even if the pre-meeting communications are considered sufficient to answer the
16 questions. Contact the RPM if there are any major changes to your development plan, the
17 purpose of the meeting, or the questions based on our preliminary responses, as we may not
18 be prepared to discuss or reach agreement on such changes at the meeting.

19
20 **Purpose of the Meeting:** To discuss the development program for tazarotene lotion, 0.045%.

21
22 **Regulatory**

23 **Question 8:**

24 The Sponsor intends to request a partial waiver for the conduct of clinical studies with IDP-123
25 Lotion in pediatric subjects aged 0-8 years 11 months due to the very low prevalence of acne in
26 this age group. The Sponsor intends to include subjects 9 YOA and above in clinical studies with

IDP-123 Lotion. The initial Pediatric Study Plan will be submitted to IND 126277 within 60 days from the date of the End-of-Phase 2 meeting date.

Does the Agency agree with the Sponsor's request for partial waiver for pediatric subjects aged 0-8 years 11 months?

FDA Response:

As discussed at the pre-IND meeting, this is reasonable. Incidence and prevalence data for various pediatric age groups should be provided in the PSP to support the waiver request.

Chemistry, Manufacturing, and Controls (CMC)

Question 1:

DPS is proposing specifications in accordance with the current International Council for Harmonisation (ICH) guideline Q6A for drug substance and drug product. Tazarotene drug substance is not described in a US Pharmacopoeia monograph. Details of the proposed specifications are provided in the briefing book (Section 1.6.2.13.1). We acknowledge that the suitability of the acceptance criteria could be an NDA review issue.

Based on the specifications provided in the briefing book, does the Agency have any recommendations regarding:

- a. the drug substance specifications

FDA Response:

In general, the submitted drug substance specifications appear reasonable. In addition to the drug substance specifications submitted, evaluate the need to control the polymorphic form of the drug substance in the specifications. Since the information for the control of starting materials, intermediates, manufacturing process, potential impurities and degradation products is all referenced to DMF (b) (4) we cannot provide detailed input on whether additional controls are necessary for other potential impurities or if additional tests will be needed in the drug substance specifications. These specific requests will be communicated to the DMF holder during review of the marketing application and you will be notified that a request has been made to the DMF holder at that time.

- b. the drug product specifications proposed for use in phase 3 clinical studies (to be conducted with the to-be-marketed formulations)?

FDA Response:

Besides the tests proposed in the drug product specification, we recommend you add a test for globule size of the lotion to the drug product specification. The test methods and acceptance criteria of the drug product specification will be evaluated during IND and NDA reviews.

- c. the ability to obtain reasonable assurance of filing and approvability of the NDA submission?

FDA Response:

See responses to a and b in Question 1.

Question 2:

For Phase 3 and registration stability, stability studies will be conducted in accordance with the current ICH guideline Q1A. For the registration stability batches, a physician's sample (3 g) and 1 trade size (45 g) will be filled into tubes. The details of the proposed stability studies and package types for the tube fill sizes are provided in the briefing book (Section 1.6.2.13.1). Note, 2 of the 3 registration stability batches have been manufactured and placed on stability. 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?

FDA Response:

Your stability program appears reasonable to support the NDA submission. You should update your drug product specification to include the recommended globule size test when conducting stability studies. Additionally, the results of extractable and leachable studies should be included in your NDA submission.

Nonclinical

Question 3:

The Sponsor intends to establish a clinical bridge to rely on the Agency's prior findings of safety for the RLD, TAZORAC Cream 0.1% (NDA 021184); this specifically includes genotoxicity, reproductive toxicity, and carcinogenicity. The preliminary results from the Phase 2 clinical bridging study (V01-123A-201, Section 1.6.2.7.4.2.3) suggest that the safety profile of IDP-123 Lotion in subjects with acne is comparable to that of TAZORAC Cream 0.1%. The preliminary results of the Phase 1 PK bridging study (V01-123A-501, Section 1.6.2.7.4.2.2) suggest that the systemic exposure of IDP-123 Lotion is similar to the RLD. For the drug product, IDP-123 Lotion, DPS intends to rely on repeat dose toxicity and local tolerance data from the nonclinical studies conducted in support of the development of IDP-118 Lotion.

Does the Agency agree that no additional nonclinical studies would be required, and that the studies for IDP-123 Lotion, coupled with the existing body of nonclinical data for TAZORAC Cream, are sufficient to support filing and registration of IDP-123 Lotion, considering that TAZORAC will be the RLD selected for a 505(b)(2) NDA?

FDA Response:

Yes, we agree that no additional nonclinical studies would be required to support a 505(b)(2) NDA for your product IDP-123 Lotion if it is determined that you have established an adequate clinical bridge to the listed drug.

Clinical

Question 4:

The bridging strategy to TAZORAC Cream 0.1% was agreed upon with the FDA at the pre-IND meeting held 17 June 2015 (meeting minutes provided in Section 1.6.2.13.2). The program

includes a PK bridging study, V01-123A-501 (preliminary results are provided in Section 1.6.2.7.4.2.2), and a safety and efficacy bridging study, V01-123A-201 (preliminary results are provided in Section 1.6.2.7.4.2.3). The results submitted in the briefing document suggest an adequate clinical bridge will be established.

Does the Agency agree that the results from the bridging studies are adequate to establish a clinical bridge to TAZORAC Cream 0.1% and allow for a successful 505(b)(2) NDA pathway for IDP-123 Lotion?

FDA Response:

You note in the briefing document (page 28) that while the clinical visit portion of the phase 2 bridging study is complete, “data analysis and interpretation are ongoing”. Based on interim results we cannot comment on the adequacy of the clinical bridge at this time. Final agreement will be made following review of the final study report and bioanalytical method validation reports at the time of NDA review.

Question 5:

The Sponsor proposes to conduct two, 12-week, vehicle-controlled, Phase 3, adequate and well-controlled studies to confirm the efficacy and safety of IDP-123 Lotion to obtain reasonable assurance of approvability from the treatment of acne in patients 9 YOA and older.

- a. Does the Agency agree that the design, endpoints, subject population, inclusion and exclusion criteria for the Phase 3 clinical studies described within the protocol are adequate to produce substantial evidence of efficacy and safety for the treatment of acne?

FDA Response:

You propose to conduct a Phase 3, Multi-Center, randomized, double-blind, vehicle-controlled, study to compare the safety and efficacy of IDP-123 Lotion (b) (4), in the treatment of acne vulgaris.

Approximately (b) (4) subjects will be randomized in a (b) (4) ratio to the following treatment groups:

(b) (4)

Co-Primary efficacy endpoints:

IDP-123 Lotion will be compared to (b) (4) and Vehicle Cream.

Co-primary endpoints are:

- Absolute change from Baseline to Week 12 in mean inflammatory lesion counts
- Absolute change from Baseline to Week 12 in mean non-inflammatory lesion counts
- Percent of subjects who achieve at least a two-grade reduction from baseline and are Clear or Almost Clear at Week 12 in the Evaluator’s Global Severity Score.

The controlled clinical studies as proposed in your briefing document would appear to be adequate to support filing of 505(b)(2) NDA for the treatment of acne vulgaris. As you are aware, approvability of such an application would be a review issue.

b. Does the Agency agree that the planned statistical analyses for the Phase 3 clinical studies described within the protocol are adequate to produce substantial evidence of efficacy and safety for the treatment of acne?

FDA Response:

Your planned statistical analyses appear reasonable. You should ensure that all the details of the statistical analysis plan are adequately pre-specified. Additional comments may be provided when completed protocols are submitted to the IND.

Question 6:

At the pre-IND meeting held 17 June 2015 (meeting minutes provided in Section 1.6.2.13.2), 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 preliminary safety and efficacy results from the Phase 2 bridging study (Section 1.6.2.7.4.2.3) and the preliminary PK results from the Phase 1 PK bridging study (Section 1.6.2.7.4.2.2) provide evidence that the safety profile and systemic exposure of IDP-123 Lotion is similar to TAZORAC Cream 0.1% and, consequently, would not require a separate long term safety study to support registration of IDP-123 Lotion.

Does the Agency agree that, based upon the available data, an adequate clinical bridge will be established and an additional long-term safety study with IDP-123 Lotion is not needed for a 505(b)(2) NDA approval?

FDA Response:

You are referred to the response to this question in the pre-IND meeting minutes, "A long-term safety study with IDP-123 lotion, 0.045% may not be required if you construct an adequate clinical bridge to Tazorac cream, 0.1%." This proposal is still reasonable assuming your study demonstrate comparable systemic exposure to Tazorac cream 0.1%

Regarding the clinical bridge, see the Agency response to Question 4 above.

Question 7:

Tazarotene formulated in TAZORAC Cream and Gel, 0.05% and 0.1%, has been approved and commercialized for use since June 1997 (TAZORAC Gel) with no associated reported cardiac events of interest (eg, torsades de pointes and cardiac arrhythmia) (Section 1.6.2.7.4.4.2). The bioavailability of IDP-123 Lotion has been shown to be similar to that of TAZORAC Cream 0.1%, based on the preliminary PK results (Section 1.6.2.7.4.2.2) from the Phase 1 bridging study that, when coupled with the lack of reported cardiac arrhythmias associated with tazarotene use, indicate a pro-arrhythmia risk is not anticipated with the use of IDP-123 Lotion. In addition, in vitro hERG and ECGs in minipigs did not reveal any safety concerns (Section 1.6.2.7.4.4.2). In the pre-IND meeting minutes (meeting minutes provided in Section 1.6.2.13.2), the FDA stated a TQT waiver is reasonable, provided that the systemic exposure from IDP-123 Lotion is similar to the systemic exposure from TAZORAC Cream 0.1%. Therefore, DPS intends to

request a waiver for conducting a clinical study with IDP-123 Lotion 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-123 Lotion is not needed for NDA filing and approval?

FDA Response:

The proposed plan is reasonable provided review of the final Phase 2 study report demonstrates that the systemic exposure from IDP-123 is similar to or lower than the systemic exposure from Tazorac cream, 0.1%.

See Agency response to Question 4 above.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

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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, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X</i>

3. <i>Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
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

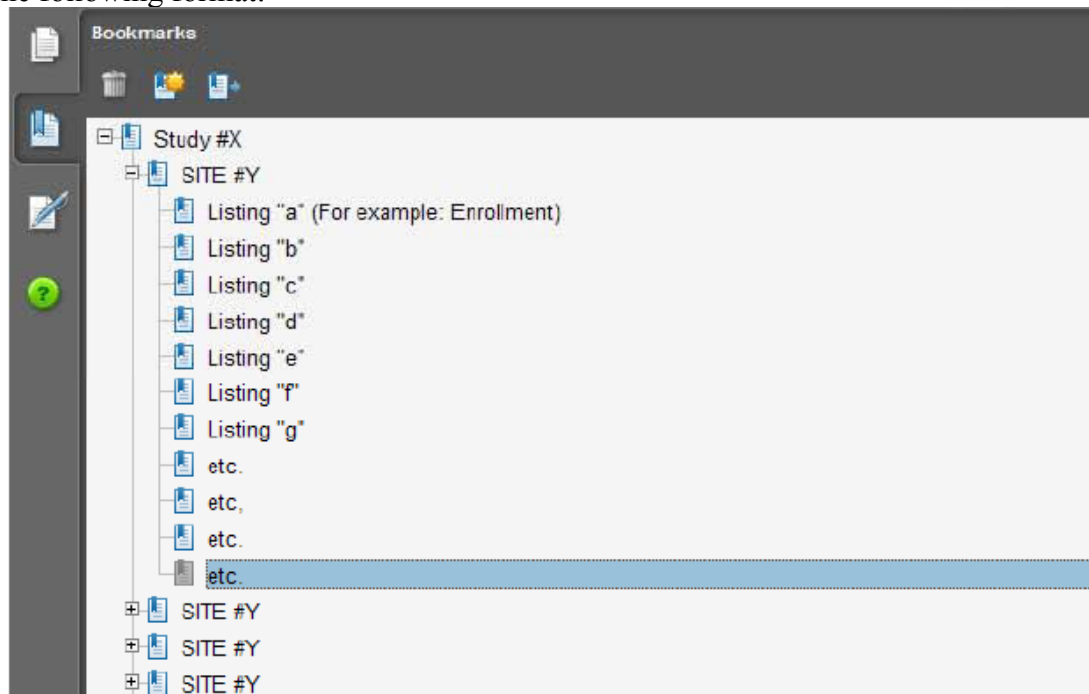
investigator's participation in the study, we request that this updated information also be provided.

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

- 462 g. By subject listing of protocol violations and/or deviations reported in the NDA,
463 including a description of the deviation/violation
464 h. By subject listing of the primary and secondary endpoint efficacy parameters or
465 events. For derived or calculated endpoints, provide the raw data listings used to
466 generate the derived/calculated endpoint.
467 i. By subject listing of concomitant medications (as appropriate to the pivotal clinical
468 trials)
469 j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
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471 2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using
472 the following format:



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

489 **Attachment 1**

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Technical Instructions:

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Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

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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

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

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- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

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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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

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

/s/

OMOLARA R LAIYEMO
12/02/2016