CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209354Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209354

MEETING MINUTES

Dow Pharmaceuticals, Inc.
Attention: Sean Humphrey
Assoc. Director, Regulatory Affairs
1330 Redwood Way, Suite C
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for halobetasol propionate and tazarotene lotion, 0.01%/0.045%.

We also refer to the meeting between representatives of your firm and the FDA on August 1, 2018. The purpose of the meeting was to discuss the Complete Response Letter, dated June 15, 2018.

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

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor Response to Meeting Preliminary Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type A
Meeting Category:	Post Complete Response Action
Meeting Date and Time:	August 1, 2018; 11:00 AM – 12:00 PM ET
Meeting Location:	FDA, White Oak Building 22 Room 1421
Application Number:	NDA 209354
Product Name:	halobetasol propionate and tazarotene lotion, 0.01%/0.045%
Proposed Indication:	treatment of (b) (4) plaque psoriasis in patients 18 years of age and older
Sponsor Name:	Dow Pharmaceuticals, Inc.
Meeting Chair:	Jill A. Lindstrom, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Jill A. Lindstrom, MD, Deputy Director, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Renqin Duan, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics (DB) III
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) III
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Jessica Weintraub, PharmD, Safety Evaluator, Division of Pharmacovigilance I
Wes Ishihara, MEM, Associate Director for Regulatory Affairs, Office of Drug Evaluation (ODE) III
Julieann DuBeau, Regulatory Scientist, ODE III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Ezra Lowe, PhD Director, Clinical Pharmacology
Gina Martin, Director, Dermatology Development

Isabelle Lefebvre, Vice President Global Regulatory Affairs, Prescription Drugs, Consumer Products, US and International Support
RK Pillai, PhD, Vice President, R&D, Head Dermatology Development
Robert Israel, MD, Sr. Vice President, Clinical/Medical Affairs
Sean Humphrey, Associate Director, Global Regulatory Affairs
Sharon A. Tonetta, PhD Vice President, Global Regulatory Affairs
Tage Ramakrishna, MD, Chief Medical Officer, President of Research and Development
William Jo, PhD, DABT, Director, Nonclinical
Bill Humphries, Executive Vice President, Ortho-Dermatologics

1.0 BACKGROUND

The purpose of the meeting is to discuss the Complete Response Letter, dated June 15, 2018.

2.0 DISCUSSION

2.1. Regulatory

Question 1:

(b) (4)

Does the Agency agree?

FDA Response to Question 1:

We do not agree. The new analysis also shows that the bioavailability of your new combination product was higher than the listed drugs. The increase in bioavailability needs to be supported by adequate pharmacology-toxicology data. See response to Question 3 and 4.

Meeting Discussion:

There was general discussion about the endpoints of relative bioavailability assessment. The Agency clarified that the relative bioavailability assessment is done by looking at the 90% confidence interval ratios of the C_{max} and AUC of the new product versus the listed drugs. Furthermore, the Agency stated that the sponsor is not expected to strictly meet the no effect boundary of 80% to 125% and if they are outside this boundary additional data may be necessary to support the safety and/or effectiveness of your product.

The sponsor inquired about what ratios provided in Tables 4 and 5 were considered when the Agency determined that the bioavailability of the product was higher than the listed drugs. The Agency clarified that both point estimates of the geometric mean ratios and the 90% confidence intervals were used.

Question 2:

(b) (4)

(b) (4) Does the Agency agree?

FDA Response to Question 2:

We do not agree. The comparative bioavailability data indicated that the bioavailability of your combination product was higher than the individual monads. Although you have provided clinical safety information for your product, you will need to address the pharmacology-toxicology elements that are stated in the response to Question 3 and 4.

Meeting Discussion:

The Agency noted that differences between the sponsor's cited precedents and their application include advancement in science, evolution of regulatory thinking, relevant dosage forms and differences in magnitude of effect.

Question 3:

(b) (4)

(b) (4) Does the Agency agree and, if not, could the Agency provide the criteria used to determine that additional nonclinical testing (as listed in the CRL) is necessary for approval and/or to establish an adequate bridge?

FDA Response to Question 3:

We do not agree (b) (4) Therefore, you cannot rely on the Agency's finding of safety for the listed drugs as reflected in the labeling for the listed drugs (including fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity). You did not submit adequate published literature that provides adequate nonclinical data required for labeling for each monad. Therefore, you need to provide sufficient nonclinical toxicology data to address the fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity of each monad for approval of your NDA as detailed in the Complete Response letter you received on June 15, 2018. See also response to Question 4.

Question 4:

(b) (4)

(b) (4)

FDA Response to Question 4:
We do not agree. You would need to establish reliance on the Agency's findings of safety for Tazorac (tazarotene) Cream, 0.1% as the listed drug for your application and generate an adequate clinical bridge to that listed drug. Additionally, you will also need to address halobetasol propionate.

For purposes of addressing fertility and reproduction, embryofetal development, genotoxicity and carcinogenicity, an adequate clinical bridge to one or more listed drugs is typically constructed through the conduct of comparative bioavailability studies with each listed drug and, for halobetasol propionate, a comparative HPA axis suppression study; comparative trials with clinical endpoints may not be necessary.

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.

Meeting Discussion:
The Agency stated that the sponsor's proposed change in regulatory pathway from a 505(b)(2) to a 505(b)(1) regulatory pathway with submission of right of reference letters for Ultravate Cream, 0.05%, Tazorac Cream, 0.05% and 0.1%, and Tazorac Gel 0.05% and 0.1% appears reasonable. The adequacy of the proposed 505(b)(1) regulatory pathway would be determined during the review of the NDA resubmission and would be dependent on the contents of the right of reference letters.

3.0 ADMINISTRATIVE COMMENTS

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.
3.0

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

/s/

JILL A LINDSTROM
08/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111218

MEETING MINUTES

Dow Pharmaceutical Sciences
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 and tazarotene lotion, 0.01%/0.045%.

We also refer to the teleconference between representatives of your firm and the FDA on February 15, 2017. The purpose of the meeting was to discuss the development program for halobetasol propionate and tazarotene lotion, 0.01%/0.045%.

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

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Meeting Minutes
Sponsor Response to Preliminary Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 15, 2017, 9:00 AM
Meeting Location:	Teleconference
Application Number:	IND 111218
Product Name:	halobetasol propionate and tazarotene lotion, 0.01%/0.045%
Proposed Indication:	For the treatment of psoriasis in adults 18 years of age and older
Sponsor Name:	Dow Pharmaceutical Sciences, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Renqin Duan, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Rebecca Hager, PhD, Statistical Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3 (DCP 3)
Yichun Sun, PhD, Acting Quality Assessment Lead, Division of New Drug Products II (DNDP II), New Drug Products Branch V (NDPB V)
Debasis Ghosh, PhD, Chemistry Reviewer, New Drug Products Branch II
Jason God, PhD, Microbiology Reviewer, Microbiology Assessment Branch II
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP
Angela Brown, MPH, Regulatory Health Project Manager, DDDP
Cecilia Robinson, MPH, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Arturo Angel, Director, Formulation and Process Development
Binu Alexander, Senior Director, Clinical Operations

Chandelle Hermes, Formulation Chemist, Formulation and Process Development
E. Kwame Obeng, Executive Director, CMC Regulatory Affairs
Ezra Lowe, Director, Clinical Pharmacology
Gina Martin, Senior Manager, Dermatology Drug Development
Isabelle Lefebvre, Vice President Regulatory Affairs, Branded & Generic Prescription Drugs, Consumer Products
Johnson Varughese, Vice President, Clinical Services
Karen Krstulich, Executive Director, Regulatory Affairs
Linda Galbier, Director, CMC Regulatory Affairs
Lindsey Mathew, Director, Clinical Operations
RK Pillai, Vice President, Dermatology Drug Development
Robert Kang, Senior Director, Data Management
Sean Humphrey, Senior Manager, Regulatory Affairs
Shruti Sahay, Director, Analytical Sciences
Simon Yeh, Senior Director, Analytical Sciences
Susan Harris, Director, Biostatistics
Tage Ramakrishna, Chief Medical Officer, President of Research and Development
William Jo, Director, Nonclinical
Zach Pfauth, Clinical Research Associate, Clinical Operations

CONSULTANTS

(b) (4)

1.0 BACKGROUND

The purpose of meeting is to discuss the development plan for halobetasol propionate and tazarotene lotion, 0.01%/0.045%.

Regulatory Correspondence History
We have had the following teleconferences with you:

- February 25, 2015 – End-of-Phase 2
- December 3, 2014 – Guidance
- July 31, 2014 – Guidance /Written Responses Only
- June 15, 2011 – Pre-IND

We have sent the following correspondences:

- June 16, 2016 – Agreed Initial Pediatric Study Plan – Agreement
- May 5, 2016 – Advice Letter
- April 27, 2016 – Pediatric Study Plan Written Response
- April 22, 2016 – Advice
- February 22, 2016 – Pediatric Study Plan Written Response
- November 9, 2015 – Initial Pediatric Study Plan Written – Incomplete
- September 8, 2015 – Advice
- July 31, 2015 – Pediatric Study Plan Advice
- January 30, 2013 – Advice/Information Request

- March 16, 2012 – Advice

2.0 DISCUSSION

2.1. Regulatory

Question 17:
The Sponsor proposes to submit the IDP-118 Lotion NDA in eCTD format with a complete XML backbone. The proposed content for Modules 1-5 is provided in Appendix 1.6.2.13.11.

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

FDA Response to Question 17:
From a technical standpoint (not content related) yes, the proposed format of the NDA as outlined in the briefing document is acceptable however, please see additional comments, below.

- For archival purposes, also submit a pdf file of the labeling document submitted in word. When you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

2.2. Chemistry, Manufacturing and Controls

Questions 1a and 1b:
Dow Pharmaceutical Sciences is proposing specifications in accordance with current ICH Q6A for drug substance and drug product. Halobetasol propionate drug substance is described in a USP monograph. Although tazarotene drug substance is not described in a USP monograph, the proposed specifications are comprehensive and based on current ICH guidelines. Details of the proposed specifications are included in Appendix 1.6.2.13.8. 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.

Question 1a:

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

FDA Response to Question 1a:
The drug substance specifications proposed for halobetasol propionate and tazarotene appear reasonable. We have no additional comments on drug substance specifications.

Question 1b:

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 1b:

The tests proposed 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:

Reference is made to the End-of-Phase 2 Meeting held on February 25, 2015, with regard to FDA response to CMC Question 1 in meeting minutes dated March 3, 2015. Specifically, the Agency recommended performing a droplet test and particle size test. (b) (4) Therefore, the particle size test is not necessary. An evaluation of (b) (4) droplet size has been performed and is discussed in Appendix 1.6.2.13.8.

Based on the data presented in the briefing document does the Agency agree that we can continue to test for (b) (4) droplet size (b) (4) ?

FDA Response to Question 2:

No. We recommend you continue to perform the test for (b) (4) droplet size on the drug product batches at release and during stability studies.

Question 3:

With regard to the drug product impurities, the maximum daily dose (MDD) and calculation for total daily intake (TDI) are provided in Appendix 1.6.2.13.8. Does the Agency agree that our approach to proposing the acceptance criteria for individual unspecified impurities (for halobetasol propionate and tazarotene related substances) is acceptable?

FDA Response to Question 3:

Your approach to proposing the acceptance criteria for individual unspecified impurities (for halobetasol propionate and tazarotene related substances) based on ICH Q3B(R2) appears reasonable.

Question 4:

Dow Pharmaceutical Sciences has conducted ICH registration stability studies in accordance with ICH Q1A guideline. The bracketing design for the ICH stability batches, a sample (3 g fill size) and 3 trade sizes (45, 60 and 100 g fill sizes), was previously proposed and accepted as per the End-of-Phase 2 Meeting held on February 25, 2015 (IND 111218, sequence 0022) and FDA response to CMC Question 3 in meeting minutes dated March 3, 2015.

For the process validation batches, the bracketing design will include the 3 g and 100 g fill sizes only. The process validation lots will be tested at long-term and accelerated conditions

(horizontal and inverted orientations) and the routine commercial batches will be tested at long-term conditions in the horizontal orientation only. The annual lots will be tested at long-term conditions only and no bracketing design is proposed. One lot of drug product (any fill size), manufactured within a given year, will be placed on stability to satisfy the annual commitment.

The details of the stability studies and package types for the tube fill sizes are provided in Appendix 1.6.2.13.8.

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 New Drug Application?
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?

FDA Response to Question 4:
The stability program based on a bracketing design proposed for the registration stability batches appears reasonable to support your NDA filing.

For the process validation batches, we recommend that the samples of the packaging configuration of 60 g be tested according to the stability protocol. For annual stability tests, one lot of each fill size should be placed on stability test at long-term conditions in accordance with the stability protocol. Additionally, the test for (b) (4) droplet size should be included in these stability protocols.

Meeting Discussion:
The sponsor requested that the Agency clarify the packaging configurations of the validation batches that should be tested in the stability studies. The Agency confirmed that the packaging configurations of the 3, 60 and 100 g should be tested in the stability studies.

Question 5:
Question 5: In addition to the ICH stability studies, the Sponsor conducted the following studies: photostability, temperature cycling (both freeze/thaw and cold/warm), in-use testing (bracketed by 45 and 100 g fill sizes), and leachable/extractables assessment on the proposed commercial container closure. A brief description of these studies is provided in Appendix 1.6.2.13.8. The results of these studies will be summarized in sections 3.2.P.2.4 Container Closure System (extractables/leachables) and 3.2.P.8.1 Stability Summary and Conclusion (remaining studies) of the NDA.

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

FDA Response to Question 5:
The studies you conducted appear reasonable to support your NDA filing. Acceptability of the study results submitted will be evaluated during NDA review.

Question 6:

Specifically, with regard to the proposed post-approval stability protocol, we intend to eliminate the antimicrobial effectiveness testing (AET) for routine production batches. As stated in ICH Q6A for antimicrobial preservative content, "antimicrobial preservative effectiveness should be demonstrated during development, during scale up and throughout shelf life per ICH Q1A, although chemical testing for preservative content is the attribute normally included in the specification." Based on the dose response testing at 100%, 80% and 60% of the (b) (4) levels and the data obtained on the ICH registration batches (as summarized in the briefing document), we believe that the (b) (4) (antimicrobial preservative content tests) are suitable surrogate tests for the AET per current USP<51>. Should the percent label claim for either (b) (4) fall below the lower shelf life limit of (b) (4) % of label claim at any interval on stability, then AET testing would be performed. Does the Agency agree that this approach is acceptable?

FDA Response to Question 6:

The proposal to eliminate AET testing for the routine batches as described for the post-approval stability protocol appears acceptable. Please note that the stability program for the registration batches should continue to include the AET testing up and including the expiry date.

Additional comments:

1. The NDA submission should also include a one-time AET study performed at or below the lowest acceptable preservative concentration to support the ability of the preservative to maintain effectiveness at the lowest label claim for preservative content.

Meeting Discussion:

The sponsor asked if the data provided to address one-time AET studies in the briefing document was acceptable. The Agency stated that the provided data appears acceptable.

2. Regarding Burkholderia cepacia:

Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

a. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process

controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

b. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

Meeting Discussion:
The Agency did not have specific recommendations for representative BCC strains to be evaluated.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.
For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

Question 7:
With regard to the proposed post-approval stability protocol, we propose (b) (4) for routine commercial production batches. (b) (4) (b) (4) (b) (4)

Does the Agency agree that this approach is acceptable?

FDA Response to Question 7:
No. Your proposal of (b) (4) for routine commercial production batches is not acceptable.

Additional CMC Comment:
The quality of diethyl sebacate, which is a NF article, should conform to all the test requirements listed in the current NF monograph.

Meeting Discussion:
The sponsor proposed to use diethyl sebacate (b) (4) The Agency reiterated that the quality of diethyl sebacate should conform to all the test requirements listed in the current NF monograph.

2.3. Pharmacology/Toxicology

Question 8:
Question 8: The IDP-118 Lotion nonclinical development program was discussed and agreed upon with the Agency at the pre-IND and EOP2 meetings. The Sponsor assessed the local and systemic toxicity of IDP-118 Lotion in a 3-month repeat dose dermal minipig toxicity, and local tolerance in skin sensitization, phototoxicity and ocular irritation studies. The Sponsor intends to reference TAZORAC Cream (0.05% and 0.1%) and ULTRAVATE Cream (0.05%) drug product labels for genotoxicity, carcinogenicity (tazarotene only) and reproductive and developmental toxicity.

Assuming that a clinical bridge to the LDs is established, does the Agency agree in principle that the nonclinical program is sufficient to support a 505(b)(2) NDA for IDP-118 Lotion?

FDA Response to Question 8:
Yes, we agree if you are able to generate adequate clinical bridge to the listed drugs.

2.4. Clinical Pharmacology

Question 12:
The Sponsor submitted a TQT waiver request February 4, 2016 (Sequence 0053). In an advice letter dated April 22, 2016 the Agency stated that a waiver would be reasonable if the results from the maximal use PK trial confirm that the systemic exposure of halobetasol propionate, tazarotene and tazarotenic acid following IDP-118 lotion treatment under maximal use conditions is low and less than or similar to those following treatment with listed drugs.

Based on PK interim data, drug bioavailability has been shown to be low and similar to that of TAZORAC Cream 0.05% and ULTRAVATE Cream 0.05%. Based on the ECG data in study V01-118A-301 no safety signals were observed.
Does the Agency agree that a waiver to conduct a TQT study to assess the potential of QT prolongation with the use of IDP-118 Lotion appears reasonable?

FDA Response to Question 12:
Because your maximal use PK trial (V01-118A-501) is still ongoing, we cannot determine whether a waiver of conducting a TQT study is reasonable at this time. You should determine whether a waiver request for a TQT study would be reasonable or not based on relative bioavailability assessment of your product under maximal use conditions compared to the listed drugs. You are referred to our communication dated 04/22/2016 which provides further information on the TQT waiver. Final determination will be made at the time of your NDA

submission following review of your study reports, bioanalytical method validation and bioanalysis reports.

Additional Clinical Pharmacology Comments:

1. Submit the relative bioavailability results by calculating the 90% confidence intervals of the geometric mean ratios for plasma peak concentrations (C_{max}) and area under the plasma concentration-time curves (AUC) of your product compared to the Listed Drugs. In your NDA submission, we recommend that you submit files containing PK data, calculated PK parameters, assessment of amount of formulations used, and serum cortisol data in transport file (.xpt) format.

2. You should submit the bioanalytical method validation reports for all analytes of interest including cortisol and bioanalysis reports for your PK trials. The bioanalysis of the study plasma samples for PK assessment and serum samples for cortisol concentration determination should be supported by adequate long term storage stability data.

3. We acknowledge that you plan to submit a report of a single point vasoconstrictor study for your product in your NDA submission. You should clearly identify the potency class of your product by comparing your product to currently marketed products with adequately bracketed potency.

4. You should address the potential for drug interactions. For further information, you are referred to draft guidance for industry: *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012).*

2.5. Clinical/Biostatistics

Question 9:
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-118 Lotion with an indication for the topical treatment of psoriasis?

FDA Response to Question 9:
The clinical development program for IDP-118 Lotion includes the following 11 studies:

- 1 Phase 1 potency study (V01-118A-101)
- 1 Phase 1, 21-day cumulative irritation study (V01-118A-102)
- 1 Phase 1 RIPT study (V01-118A-103)
- 1 Phase 1 maximal use PK and bridging study between IDP-118 Lotion and both

ULTRAVATE Cream, 0.05% and TAZORAC Cream, 0.05% (V01-118A-501)

- 1 Phase 2 proof of concept study (DPS-IDP-118-P2-01)
- 1 Phase 2 safety and efficacy study comparing IDP-118 Lotion with its monads and vehicle (V01-118A-201)

- 1 Phase 2 bridging study between IDP-118 Lotion and TAZORAC Cream, 0.05% (V01-118A-202)
- 1 Phase 2 bridging study between IDP-118 Lotion and ULTRAVATE Cream, 0.05% (V01-118A-203)
- 2 Phase 3 safety and efficacy between IDP-118 Lotion and Vehicle Lotion (V01-118A-301 and V01-118A-302)
- 1 Phase 3 long term safety study (V01-118A-303)

The outlined clinical development program appears to be adequate to support a marketing application.

Question 10:
A total of approximately 1900 human subjects will have been exposed to at least 1 dose of IDP-118 under IND 111218 and will be included in the NDA submission as part of the safety database. Of these, approximately 1050 are patients with psoriasis and treated with the to-be-marketed formulation of IDP-118 Lotion, with at least 325 exposed for a minimum of 6 months and approximately 100 exposed for 1 year (from the long-term safety study, V01-118A-303), therefore, the number of exposures has been met in accordance with the requirements of the 1995 ICH E1A Guidance, *"The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions."*

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

FDA Response to Question 10:
The information pertaining to total patient exposure appears to be consistent with the numbers recommended in the E1A guideline and to support a marketing application. Provide more specific information regarding the number of subjects exposed for one year (stated as "approximately 100").

Question 11:
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 11:
Yes.

Question 13:
For the two pivotal Phase 3 studies (V01-118A-301 and V01-118A-301) as well as the long-term safety study (V01-118A-303) the Sponsor plans to submit Case Report Forms (CRFs) in Appendix 16.3 by site and patient identifier. CRFs for the following subjects will be submitted in the NDA:

- Deaths during the study(s)
- Other Serious Adverse Events during the study(s)
- Discontinued due to an Adverse Event during the study(s)

Does the Agency agree with the CRFs the Sponsor proposes to submit in the NDA for the pivotal phase 3 studies and the long-term safety study?

FDA Response to Question 13:
This is acceptable. Also, be prepared to supply any additional CRFs upon request and with a rapid turnaround. Additionally, submit narrative summaries for all of these same categories of events.

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:

- V01-118A-301 (Phase 3 safety and efficacy)
- V01-118A-302 (Phase 3 safety and efficacy)
- V01-118A-303 (Phase 3 long term safety)
- V01-118A-201 (Phase 2 safety and efficacy)
- V01-118A-202 (Phase 2 safety and efficacy bridge to TAZORAC Cream)
- V01-118A-203 (Phase 2 safety and efficacy bridge to ULTRAVATE Cream)
- V01-118A-501 (Phase 1 maximal use PK bridge to TAZORAC and 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] and DPS-IDP-118-P2-01 [proof of concept]) 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 14:
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 comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. 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).

Meeting Discussion:
The sponsor agreed to submit SAS excerpts to conduct the multiple imputation and analysis of the primary and secondary endpoints as well as the sensitivity analyses.

Question 15:
Statistical analysis of the safety data for the Phase 3 studies V01-118A-301 and V01-118A-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 1.6.2.13.9. 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:
The statistical analysis plan for the integrated summary of safety (ISS) appears reasonable.

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 is acceptable.

Also, provide your plans for the 120-day Safety Update.

Question 16:
Statistical analysis of the efficacy data for the Phase 3 studies V01-118A-301 and V01-118A-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 1.6.2.13.10. 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:
The statistical analysis plan for the integrated summary of efficacy (ISE) appears reasonable.

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 is acceptable.

3.0 ADMINISTRATIVE COMMENTS

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. 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.

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.

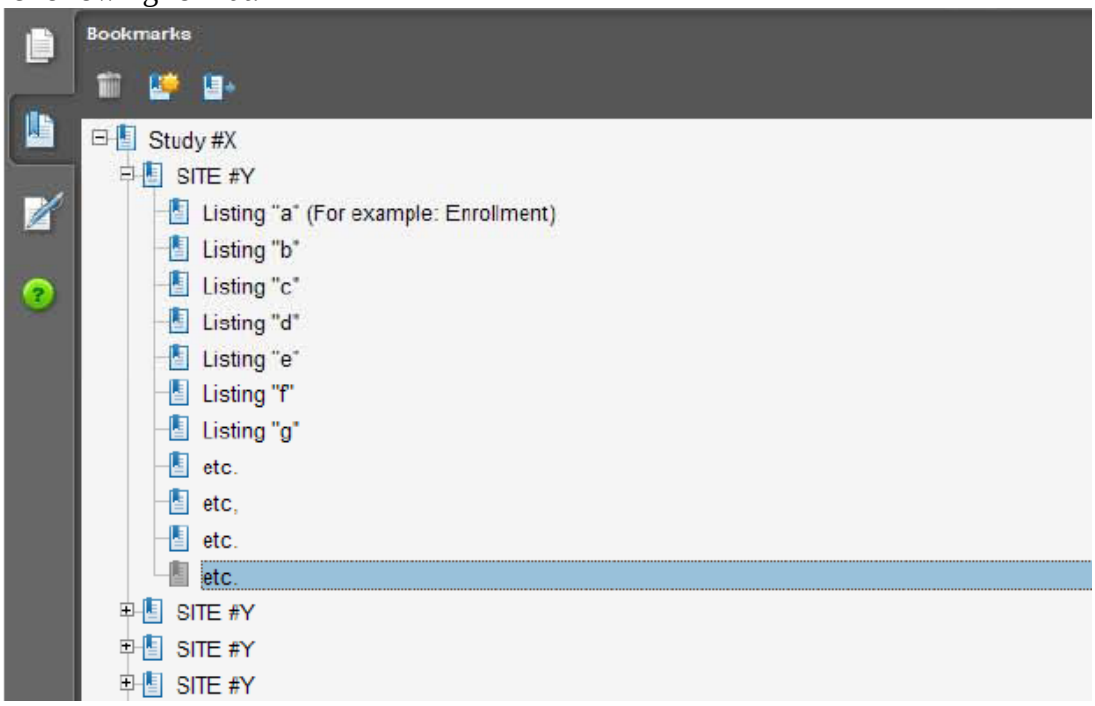
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

Reference ID: 4462882

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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."

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

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

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.

[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

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

KENDALL A MARCUS
03/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND111218

MEETING MINUTES

Dow Pharmaceutical Sciences
Attention: Sean Humphrey
Manager, Regulatory Affairs
1330 Redwood Way
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 and tazarotene lotion, 0.01%/0.045%.

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2015. The purpose of the meeting was to discuss the development plan for halobetasol propionate and tazarotene lotion, 0.01%/0.045%.

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

If you have any questions, call Strother D. Dixon at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Acting Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase-2
Meeting Date and Time:	February 25, 2015, 9:00 AM EST
Meeting Location:	FDA, White Oak Building 22
Application Number:	IND 111218
Product Name:	halobetasol propionate and tazarotene lotion, 0.01%/0.045%
Proposed Indication:	For the treatment of psoriasis in adults 18 years of age and older
Sponsor Name:	Dow Pharmaceutical Sciences
Meeting Chair:	David Kettl, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES
David Kettl, MD, Acting Deputy Director, DDDP
Jill Lindstrom, MD, FAAD, Clinical Team Leader, DDDP
Brenda Carr, Clinical Reviewer, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
An-Chi Lu, MS, PharmD, Clinical Pharmacology Reviewer, DCP3
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Binu Alexander, Director, Clinical Development
RK Pillai, Head, Dermatology Development
Sean Humphrey, Manager, Regulatory Affairs
Steve Knapp, Executive Director, Regulatory Affairs
Tage Ramakrishna, Chief Medical Officer
(b) (4)
(b) (4) Consultant Dermatologist

Purpose of the Meeting:
To discuss the development plan for (halobetasol propionate and tazarotene) lotion, 0.01%/0.045%

Regulatory Correspondence History

We have had the following teleconferences with you:
- December 3, 2014 – Guidance
- July 31, 2014 – Guidance /Written Responses Only
- June 15, 2011 – Pre-IND

We have sent the following correspondences:
- January 30, 2013 – Advice/Information Request
- March 16, 2012 – Advice

Chemistry, Manufacturing and Controls (CMC)

Question 1:
Dow Pharmaceutical Sciences is proposing specifications in accordance with the current ICH Q6A for drug substance and drug product. Tazarotene is not described in a compendial monograph; whereas halobetasol propionate meets the requirements set forth in the current United States Pharmacopeia monograph for this drug substance.

Based on the specifications provided in this briefing book, does the Agency have any concerns or suggestions for the drug substance or drug product specifications proposed for use in Phase 3 and to support the NDA submission?

Response:
The specification for halobetasol propionate is reasonable for Phase 3 clinical study and to support the NDA submission. A second identification test should be included in the specification for tazarotene drug substance. Additionally, particle size analysis of tazarotene should be included in its specification (b) (4).

Additional tests recommended to be included in the drug product specification are droplet test, microscopic evaluation of the drug product and particle size analysis of the APIs in the drug product ((b) (4)).

Questions 2 and 3:
For Phase 3 and registration stability, stability studies will be conducted in accordance with the current ICH Q1A. Currently, 2 suppliers of tazarotene are proposed for use in the IND. Dow Pharmaceutical Sciences may also commercialize the drug product using both manufacturers. For the registration stability batches, a physician's sample (3 g fill size) and 3 trade sizes (45, 60, and 100 g) are proposed by filling various amounts of lotion in the tubes. The details of the proposed stability studies, package types and the bracketing design for the tube fill sizes are provided in the briefing book. A total of 4 bulk lots will be manufactured: 3 lots will use drug substance from the primary supplier of tazarotene and a fourth lot will be made with the secondary supplier of tazarotene. A summary of the bracketing design for 25°C/60% relative humidity (RH) is shown in Table 28. Similar bracketing designs are proposed for 30°C/65%RH through 12 months and 40°C/75%RH through 6 months.

Table 28. Summary of Bracketing Design for Each Bulk Lot at 25°C/60%RH (proposed commercial configurations)

Tube Fill Size (g)	Test Interval (months)								
	0	1	3	6	9	12	18	24[a]	36
45	T	T	T	T	T	T	T	T	T
60	(T)	(T)	(T)	(T)	(T)	(T)	(T)	(T)	(T)
100	T	T	T	T	T	T	T	T	T

T = stability testing will be performed; (T) = samples will be placed on stability but will not be tested
In the event of failure, the expiry for the least stable extreme will be applied.
a Testing beyond this interval is optional.

Question 2:
Does the Agency concur that to satisfy the ICH stability requirements for drug product, 3 drug product batches using the primary supplier of tazarotene and a fourth drug product lot using the alternative tazarotene supplier is sufficient to satisfy the ICH Q1A stability requirements, thus allowing both manufacturers to be listed as viable suppliers in the NDA?

Response:
Yes.

Question 3:
Based on the information provided in this briefing book, does the Agency agree that the bracketing design for the 45, 60, and 100 g fill sizes is sufficient to meet the requirements for the ICH registration stability lots?

Response:
Yes.

Additional CMC Comment:
Provide representative samples in proposed commercial packaging configurations to determine if the drug product can be classified as a lotion.

<u>Pharmacology/Toxicology</u>

Question 4:
The Sponsor has assessed the systemic and local toxicity of IDP-118 Lotion in a 3-month dermal toxicity minipig bridging study (GLP). The Agency indicated at the pre-IND meeting, and in a subsequent advice letter, that additional nonclinical studies may be needed if new safety issues become apparent after review of this study. The final report will be submitted to the IND and the audited study results are summarized in this briefing document.

Target organs of toxicity were consistent with those reported for the tazarotene and halobetasol propionate RLDs, and no new toxicities were identified for the combination product.

Does the Agency agree that no additional IDP-118 Lotion combination toxicity studies will be required?

Response:
We agree that no additional nonclinical toxicity studies with your combination drug product IDP-118 Lotion will be required based on the summary data provided in the briefing document. The final determination will be made after review of the full study report for your 3-month dermal minipig study.

Question 5:
The Sponsor has conducted repeat dose toxicity and local tolerance studies with IDP-118 Lotion. As mentioned in prior interactions with the Agency, the Sponsor intends to reference Tazorac Cream (0.05% and 0.1%) and Ultravate Cream (0.05%) drug product labels for genotoxicity, carcinogenicity (tazarotene only) and reproductive and developmental toxicity, and does not intend to conduct additional nonclinical studies.

Assuming that a clinical bridge to the RLDs is established, does the Agency agree in principle that the nonclinical program is sufficient to support a 505(b)(2) NDA for IDP-118 Lotion?

Response:
We agree in principle that your nonclinical program appears sufficient to support a 505(b)(2) NDA for your combination drug product IDP-118 Lotion if you are able to establish an adequate clinical bridge to the listed drugs. Also refer to response to Question 4.

Clinical Pharmacology

Question 7:
The Sponsor has planned to conduct a comparative PK (b) (4) study designed to evaluate under maximal exposure conditions the systemic exposure of halobetasol propionate, tazarotene, and tazarotenic acid metabolite from IDP-118 Lotion, and to compare the exposure with that from Ultravate Cream and Tazorac Cream; HPA axis suppression will also be evaluated for subjects in the IDP-118 and Ultravate Cream arm. In addition, the halobetasol propionate monad will also be evaluated for purposes of potential future development of the monad as a standalone entity. The protocol synopsis included herein has been revised based on previous discussions with the Agency.

Does the Agency agree that the protocol synopsis and design of the planned PK (b) (4) study is acceptable?

Response:
We have the following comments:

1. We recommend that the disease severity at time of the applied dose at Week 2, 4, and 8 be recorded.
2. Administration of cosyntropin to the same patient repeatedly at intervals of less than 4 weeks may result in higher stimulated cortisol levels after each successive cosyntropin injection, leading to invalid data. Therefore the cosyntropin testing should be performed

no more than every 4 weeks in duration. For Ultravate treatment arm, we recommend that you separate screening and start of dosing by at least 2 weeks to allow for the 4 weeks window.

Meeting Discussion:
The sponsor inquired whether IGA scale assessment at weeks 2, 4, and 8 would be adequate for disease severity assessment. The Agency concurred with this approach.

Clinical/Biostatistics

Question 6:
The Sponsor proposes to conduct the planned clinical studies described within this briefing document to further evaluate the safety and efficacy of IDP-118 Lotion, applied once daily for 8 weeks, in the treatment of plaque psoriasis in adults 18 years of age and older. The clinical development plan is expected to include a minimum of 700 subjects exposed to the to-be-marketed formulation of IDP-118 Lotion.

a. Does the Agency agree that the 2 Phase 3 studies proposed herein are appropriately designed in terms of clinical study endpoints, subject population, inclusion and exclusion criteria, and statistical analyses in order to serve as the 2 adequate and well-controlled clinical studies for the 505(b)(2) NDA?

b. Does the Agency agree in principle that the complete clinical development plan proposed herein is sufficient to support approval of IDP-118 Lotion as indicated following the 505(b)(2) NDA regulatory pathway?

c. Does the Agency agree that the numbers of subjects included in the clinical development plan are sufficient for the evaluation of safety?

Response:
a. You seek agreement on the endpoints, subject population, inclusion and exclusion criteria, and statistical analyses for the 2 Phase 3 studies as proposed in the briefing document.

Endpoints
The primary efficacy endpoint will be the percent of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to "Clear" or "Almost Clear" on the scale below.

Investigator's Global Assessment (IGA)

Grade	Score	Description
Clear	0	No evidence of scaling No evidence of erythema No evidence of plaque elevation above normal skin level
Almost Clear	1	Some plaques with fine scales Faint pink/light red erythema on most plaques Slight or barely perceptible elevation of plaques above normal skin level
Mild	2	Most to all plaques have some fine scales but are not fully covered, some plaques are completely covered with fine scale Most to all plaques are pink/light red to bright red in color Some plaques have definite elevation above normal skin level, typically with edges that are indistinct and sloped on some of the plaques
Moderate	3	Some plaques are at least partially covered with a coarse scale, most to all plaques are nearly covered with fine or course scale; Most to all plaques are bright red, some plaque may be dark red in color Definite elevation of most to all plaques; rounded or sloped edges on most of the plaques
Severe	4	Most to all plaques are covered with coarse, thick scales Most or all plaques are bright, dark or dusky red Almost all plaques are raised and well-demarcated; sharp edges on virtually all plaques

Your proposed primary endpoint as measured on the provided scale (above) appears to be acceptable.

You propose the following secondary efficacy endpoints:

- (b) (4)
- % of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at week 12 for IDP-118 Lotion verses IDP-118 Vehicle Lotion and IDP-118 Monad (HP 0.01%) Lotion versus IDP-118 Vehicle Lotion
- % of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at week 4 for IDP-118 Lotion verses IDP-118 Vehicle Lotion
- % of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at week 2 for IDP-118 Lotion verses IDP-118 Vehicle Lotion
- % of subjects who show at least a 2 grade improvement and reach Clear to Almost Clear at wee (b) (4) for IDP-118 Monad (Taz 0.045%) Lotion verses IDP-118 Vehicle Lotion

We recommend that secondary endpoints be clinically relevant, limited in number and supportive of the primary endpoint.

Subject Population:
You propose to include subjects at least 18 years of age with an area of plaque

psoriasis appropriate for topical treatment and that covers a body surface area of at least 3%, but no more than 12%. Subjects should have an IGA score of 3 or 4 (The face, scalp, palms, soles, axillae and intertriginous areas are to be excluded in the determination of BSA and IGA).

Your study population appears to be acceptable.

b. You present a clinical development program consisting of the following 8 studies:

- DPS-IDP-118-P2-01: a Phase 2, proof-of-concept, dose/regimen exploration study (completed)
- V01-118A-201: a Phase 2 safety and efficacy of IDP-118 Lotion relative to its monads and the IDP-118 vehicle (ongoing)
- (b) (4)
- a study evaluating the safety and efficacy of IDP-118 Lotion relative to Tazorac Cream, 0.05% and the IDP-118 vehicle (planned)
- a study to evaluate the potency ranking of IDP-118 Lotion using visual and/or chromometer assessments of the vasoconstriction response to corticosteroid formulations of different potency rankings (planned)
- an RIPT study (planned)
- V01-118A-301/302: 2 Phase 3 evaluations of safety and efficacy; these will be identically designed, 4-arm studies comparing IDP-118 Lotion with its monads and the IDP-118 vehicle (planned)

Of these 8 studies, you have identified the following as the "bridging" studies:

(b) (4)

It is not clear that the clinical development plan as described would support approval of an NDA via the 505(b)(2) NDA regulatory pathway. It is not clear that your approach would adequately establish a clinical bridge to Ultravate cream. We have previously advised you that:

In order to rely on FDA's previous finding of safety for an approved product, you will need to construct an adequate clinical bridge to that product. More than one bridge may be constructed, but each bridge must be adequate in order to allow you to rely on the desired FDA findings for the approved product. An adequate clinical bridge is generally built by demonstration of comparative bioavailability; for a topical product not intended

for systemic distribution this is accomplished through conduct of well-controlled trials with clinical endpoints. For topical corticosteroids and retinoids, it would also include an assessment of comparative systemic exposure, and, for a topical corticosteroid, assessment of the effect of the product on the HPA axis.

(See pre-IND meeting minutes dated July 5, 2011 and Written Responses dated July 31, 2014).

(b) (4)

Meeting Discussion:
The sponsor proposed (b) (4)

(b) (4)

The Agency commented that this was a new proposal that was not captured in the briefing document. There was general discussion regarding trial design. (b) (4)

The sponsor will consider this issue and submit a proposal to the IND for review. Also, see our responses to Questions 3 and 4.

c. You anticipate that the clinical development plan will include a minimum of 700 subjects exposed to the to-be-marketed formulation of IDP-118 Lotion. This number of subjects may form the basis of the safety database. However, adequacy of the safety database is not merely a function of the numbers of subjects. That is, the types of information obtained from evaluation of study subjects also determines the adequacy of the safety database, e.g., dermal safety, duration of exposure.

Question 8:

(b) (4)

(b) (4)

Does the Agency agree (b) (4)?

Response:
We do not agree. (b) (4)

(b) (4) We again remind you that psoriasis is a chronic indication. You have not described your plans for adequately addressing safety data needs from long term use of your product. We again refer you to the guideline for industry *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions*.

(b) (4)

(b) (4)
"
Information pertaining to use of the active ingredients as monotherapies may not adequately support the long-term safety of those active ingredients in a combination product such as IDP-118 Lotion.

We note that the top-line results you provided from study V01-118A-201 include apparent steroid-related adverse events (atrophy and telangiectasias) after an 8-week treatment course with IDP-118 Lotion. In fact, these signs were even reported at Week 4. This supports the need for information pertaining to the long-term safety of IDP-118 Lotion.

Meeting Discussion:
The sponsor noted the need to address long term safety. They proposed a single arm, multi-center, open label, "safety-only" clinical study (b) (4) This study would be conducted separately from and in parallel to the two Phase 3 clinical efficacy and safety studies.

(b) (4)

The Agency commented that the number of subjects were consistent with those proposed for long term safety studies. The Agency was concerned that the population should primarily include subjects with moderate to severe plaque psoriasis. The protocol with supporting rationale should be submitted to the Agency for review.

Question 9:
Tazarotene absorbs in the 290-700 nm range (peak at approximately 351 nm) and has a molar absorptivity of > 30000 L/mol·cm. (b) (4)

Does the Agency agree (b) (4) ?

Response:
You discuss peak absorption of tazarotene (above). On p. 72 of your briefing document, you state (b) (4) Also, dermal safety testing (including photosafety testing) is based on the final product not just the active ingredients. We did not find that you discussed the absorption spectrum for your product; you should provide this information in full, i.e. not just the peak absorption. (b) (4)

Question 10:
The Sponsor requests a partial waiver for the conduct of clinical studies with IDP-118 Lotion in pediatric subjects aged 0 (b) (4) , the prevalence of psoriasis in pediatric subjects is low relative to adults, the mean age of first onset is typically between 15 and 20 years of age, and the prevalence of psoriasis increases with increasing age. (b) (4)

Does the Agency agree with the Sponsor's request for a partial waiver to conduct clinical studies with IDP-118 Lotion in pediatric subjects aged 0- (b) (4) months and the deferral of clinical studies in pediatric subjects aged (b) (4) 17 years 11 months?

Response:
A partial waiver may be acceptable for the conduct of clinical studies with IDP-118 Lotion in pediatric subjects aged 0- (b) (4) months. You should discuss your plans for pediatric development in your initial pediatric study plan and include your rationale and adequate supporting information for any proposed waiver(s). Include your waiver request in the

marketing application, along with your rationale and supporting information. Note the timeline for the pediatric study plan submission in the Administrative Comments below.

Question 11:

(b) (4)

Response:
Establishing the contribution of the monads does not need to be replicated in your Phase 3 trials, taking into account that your Phase 2 trial evaluated the contribution of the monads. Therefore, your Phase 3 trials can have a simpler, two arm design with a smaller total number of subjects to demonstrate superiority of the combination product over vehicle.

You stated that the Phase 3 trials are planned with the objective of evaluating IDP-118 relative to its monads and its vehicle. In addition, you plan to compare the HP 0.01% monad to vehicle and stated that this comparison is "primarily being done for purposes of potential future development of the monad as a standalone entity." This proposal has not been previously discussed with the Agency. If your trials are intended to establish an efficacy claim for the HP 0.01% monad in addition to IDP-118, then a multiplicity adjustment would be needed to control the Type I error rate and replication of study findings would be needed to establish an efficacy claim (see above comment regarding trial design). If you plan a distinct development program for a halobetasol product, you should submit your proposal for review.

For establishing an efficacy claim for the combination product, comparisons of the monads against the vehicle do not need to be statistically significant. However, interpretation of study findings could be problematic if efficacy results for a monad are similar to that of the vehicle.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this

End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

5. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

6. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) 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.

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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

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/s/

DAVID L KETTL
03/03/2015