CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210361Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104160

MEETING MINUTES

Dermira, Inc.
Attention: Christine Conroy, PharmD
Sr. Vice President, Regulatory Affairs
275 Middlefield Road, Suite 150
Menlo Park, CA 94025

Dear Dr. Conroy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycopyrrolate topical wipes.

We also refer to the meeting between representatives of your firm and the FDA on February 8, 2017. The purpose of the meeting was to discuss the development program for glycopyrrolate topical wipes.

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 Belainesh Robnett, Regulatory Healthy Project Manager at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 8, 2017; 8:30 a.m. (ET)
Meeting Location:	White Oak Campus; Bldg. 22
Application Number:	IND 104160
Product Name:	glycopyrrolate topical wipes
Proposed Indication:	Treatment of axillary hyperhidrosis in adults and children 9 years of age and older
Sponsor Name:	Dermira, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Belainesh Robnett

FDA ATTENDEES
Julie Beitz, MD, Director, Office of Drug Evaluation III
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Melissa Reyes, MD, Clinical Reviewer, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biopharmaceutics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Rebecca Hager, PhD, Biostatistics Reviewer, DB III
Marilena Flouri, PhD, Biostatistics Reviewer, DB III
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III
Yichun Sun, PhD, Acting Quality Assessment Lead, Division of New Drug Products II, New Drugs Products Branch V
Friedrich Burnett, PhD, Staff Fellow, Division of New Drug API, New Drug Branch II
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Eugene A. Bauer, MD, Chief Medical Officer, Dermira
Janice Drew, MPH, Sr. Vice President, Clinical & Project Management, Dermira
Hans Hofland, PhD, Vice President, Research, Dermira
Delphine Imbert, PhD, Sr. Vice President, Pharmaceutical Sciences, Dermira

(b) (4) Clinical Consultant, Dermira
Luis Peña Chief Development Officer, Dermira
(b) (4) Biostatistical Consultant, Dermira
Christine Conroy, PharmD, Sr. Vice President, Regulatory Affairs,
Diane Ingolia, PhD, Sr. Director, Regulatory Affairs Dermira
Lydie Yang, MA, Director, Regulatory Affairs, Dermira
Emily Ip, PhD, Sr. Director, Project Management, Dermira
Victoria Herbert, MS, Senior Regulatory Affairs Specialist, Dermira

1.0 BACKGROUND

The purpose of the meeting is to discuss the development program for glycopyrrolate topical wipes and submission of a New Drug Application (NDA) for the treatment of axillary hyperhidrosis in adults and children 9 years of age and older.

Most Recent FDA Regulatory Correspondence History

11/30/2016	Advice
10/20/2016	Advice
09/20/2016	Advice
09/20/2016	Written Response
05/23/2016	Pediatric-Inadequate PPSR
10/01/2015	Written Response
08/20/2015	Advice
06/30/2015	Advice

2.0 DISCUSSION

2.1. Regulatory

Question 9.5.1.:
Dermira conducted a maximum-use PK trial, DRM04-HH07, to establish a clinical bridge to Cuvposa, the Listed Drug, based on exposure levels with DRM04 (glycopyrronium) Topical Solution, 2.4% and Cuvposa to permit reliance upon Cuvposa for certain nonclinical findings and information related to the metabolism, elimination, and use of glycopyrronium in subjects with renal and hepatic impairment. A table illustrating the sections of the Cuvposa label that will be relied upon is provided in Section 10.4.1. Does FDA agree that submitting the DRM04 (glycopyrronium) Topical Solution, 2.4% NDA under section 505(b)(2) using Cuvposa as the Listed Drug is appropriate?

FDA Response:
Your proposal to submit a 505(b)(2) application using Cuvposa Oral Solution (NDA 022571) as the listed drug upon which to rely for approval appears reasonable. However, a sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for a listed drug(s) should make the final determination of which listed drug(s) is/are the most appropriate for their development plan.

Question 9.5.2.:
Based on information from the evaluation of the clinical safety of DRM04 (glycopyrronium) Topical Solution, 2.4.% in clinical trials and previous findings of safety and efficacy for Cuvposa (glycopyrrolate), the Listed Drug, Dermira anticipates that potential safety risks and management of these risks can be adequately communicated to prescribers via labeling. Dermira also intends to prepare a patient information leaflet and instructions for use as part of labeling to educate and instruct patients about the appropriate use of DRM04 (glycopyrronium) Topical Solution, 2.4%. Therefore, Dermira does not plan to submit a Risk Evaluation and Mitigation Strategy (REMS) in the NDA. Does FDA agree with this plan?

FDA Response:
Based on our current understanding of your development program, a REMS program is not currently being contemplated for your proposed application. A final determination regarding the necessity of a REMS and the specifics and adequacy of labeling will occur during the review of the complete application.

Question 9.5.3.1:
Comprehensive clinical, nonclinical, and CMC data are available to support the use of DRM04 (glycopyrronium) Topical Solution, 2.4% for the treatment of axillary hyperhidrosis in adults and children ≥ 9 years of age. Dermira plans to submit a NDA for DRM04 (glycopyrronium) Topical Solution, 2.4% utilizing the 505(b)(2) regulatory pathway with Cuvposa as the Listed Drug. A table of contents (TOC) for a complete NDA is described in Section 10.4.2 and Appendix 9. Does FDA have comments on the TOC?

FDA Response:
From a technical standpoint, yes, the eCTD TOC for the planned NDA is generally acceptable. However, the additional nodes created beyond what is in the specification, specifically, within sections 3.2.R should not be used. Instead, use clear and descriptive leaf titles under 3.2.R to differentiate between sections.

All Module 4 Literature References should reside in m4.3 only and Module 5 Literature References in m5.4 only.

Question 9.5.3.2:
Dermira is considering submitting a draft audited report for the dermal carcinogenicity study of DRM04 (DRM04-TOX-14-04) with the initial NDA (see Section 10.4.2). The final study report and the datasets would then be provided within 30 days of initial submission. Would this proposal be acceptable to FDA?

FDA Response:
Applications should be complete at the time of submission.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 9.1.1.:

a. Based on release and stability data collected to date (up to 36 months), Dermira is proposing to include the following attributes in the commercial specification for glycopyrronium tosylate monohydrate: appearance, identification (by two methods), glycopyrronium tosylate monohydrate assay, water content, residue on ignition, organic impurities assay, (b) (4) assay, (b) (4) assay, and microbiological enumeration tests per USP <61> and tests for *Staphylococcus aureus* and *Pseudomonas aeruginosa* per USP <62>. Does FDA have comments regarding the adequacy of the test attributes listed in the proposed commercial specification for the drug substance to support release and stability of commercial batches?

FDA Response:
In general, the scope of the tests appears reasonable to support release and stability of the commercial batches. However, include in the specifications the test for Elemental Impurities (USP<232> and USP<233>) and follow the guidelines for reporting of individual metals such as (b) (4) or provide justification in the NDA on why these tests do not need to be performed. A test for Residual Solvents should be added as well.

b. Based on release and stability data collected to date (up to 36 months), Dermira is proposing limits for each of the test attributes in the commercial specification for glycopyrronium tosylate monohydrate drug substance. Does FDA have comments on the proposed acceptance criteria for the listed test attributes in the proposed specification for commercial batches of drug substance?

FDA Response:
In general, the limits appear reasonable, however, the final determination is an NDA review issue and the decision will be made at that time. The tests for Elemental Impurities and Residual Solvents should be included in the tests. Justification to delete these tests can be provided in the NDA for review.

Question 9.1.2.:

a. Based on scientific rationale, experimental data, release and stability data collected up to 24 months, Dermira is proposing to include the following attributes in the commercial specification for DRM04 (glycopyrronium) Topical Solution, 2.4%: appearance for container, wipe applicator and solution, package integrity, identification of glycopyrronium tosylate (by two chromatographic procedures), glycopyrronium assay, related substances assay, apparent pH, microbial enumeration test per USP <61>, test for *Staphylococcus aureus* and *Pseudomonas aeruginosa* per USP <62>, and weight loss. Based on the data available to date, does FDA have comments regarding the adequacy of the test attributes listed in the proposed commercial specification for the drug product to support release and stability of commercial batches?

FDA Response:
The test attributes proposed in the drug product specification appear reasonable to support release and stability tests of commercial batches of the drug product. The test methods of the drug product specification will be evaluated during NDA review.

b. Based on release and stability data collected to date (up to 24 months), Dermira is proposing limits for each of the test attributes in the commercial specification for DRM04 (glycopyrronium) Topical Solution, 2.4%. Does FDA have comments on the proposed acceptance criteria for the listed test attributes in the proposed specification for commercial drug product?

FDA Response:
We remind you that the acceptance criterion for Any Unspecified Related Substance should conform to the identification threshold recommended in ICH Q3B (R2). The acceptance criteria of the drug product specification need to be further evaluated during NDA review.

Additional CMC Comment:
The dosage form of your drug product will be decided during NDA review.

Meeting Discussion:
The sponsor inquired about the possible dosage form of the drug product and the timeline of receiving the decision of the dosage form designation of the product.

The Agency stated that the dosage form of the drug product will be decided by the labeling and nomenclature committee in CDER during NDA review.

2.3. Pharmacology/Toxicology

Question 9.2.1.:
Summaries of the nonclinical pharmacology, pharmacokinetics and toxicology studies planned for inclusion in the NDA are provided in Section 10.2 and Appendix 2. These studies include those conducted by the Sponsor as well as certain nonclinical studies and findings that the Sponsor will rely upon by reference to Cuvposa as the Listed Drug under section 505(b)(2) (see Section 10.4.1,Table 21). The Sponsor believes that the nonclinical package is adequate to support an NDA for the proposed indication, and that no additional nonclinical studies are warranted at this time. Does FDA agree that the nonclinical data package is sufficient to support NDA review?

FDA Response:
In principle, the described approach to addressing nonclinical issues appears to be viable, provided that an acceptable clinical bridge is established between the new product and Cuvposa. If an acceptable clinical bridge is not established to a listed drug(s), then an NDA for the proposed product should be supported by complete nonclinical information, as discussed in the ICH M3(R2) document. The adequacy of an NDA submission will be evaluated within the context of CDER's policies that pertain to filing of NDAs. The adequacy of the nonclinical database will be a review issue under the NDA.

2.4. Clinical/Biostatistics

Question 9.3.1.:

a. Does FDA find it reasonable to interpret the results from the DRM04-HH04 and DRM04-HH05 trials as providing sufficient evidence of efficacy for DRM04 (glycopyrronium) Topical Solution, 2.4% in the treatment of axillary hyperhidrosis to support NDA review?

FDA Response:
Your completed trials appear adequate for filing of an NDA application. Interpretation of the results and assessment of the risk/benefit determination would be based on the totality of evidence from the clinical trials. Determination of whether findings from the clinical trials provide sufficient evidence to support approval would be a review issue.

b. Does FDA find it reasonable that the prespecified, extreme outlier sensitivity analysis results ($p = 0.001$) can be considered in the assessment of efficacy of DRM04 (glycopyrronium) Topical Solution, 2.4% for gravimetrically-measured sweat production in the DRM04-HH04 trial?

FDA Response:
Your sensitivity analysis along with other sensitivity analyses that we may conduct would be helpful in interpreting trial findings.

c. Does FDA recommend additional analyses or data presentations with regard to the outlier data?

FDA Response:
At this stage and without access to the data, we do not currently recommend any additional analyses with regard to the outlier data.

Question 9.3.2.:
Topical glycopyrronium has been generally well tolerated (b) (4) (b) (4) As a result, Dermira proposes Does FDA find this approach reasonable?

FDA Response:
No, we do not agree to this approach. Primary axillary hyperhidrosis is a chronic disease and repeated use of your product is anticipated. Your dosage form necessitates assessments of both systemic and local safety.

As previously discussed at the End of Phase 2 meeting, you will need to sufficiently address the long term safety of your specific product, with sufficient subject exposures with duration of exposure to inform safety for eventual labeling.

For the number of subjects to be exposed to the investigational product, you are again referred to ICH guideline for industry, *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment Non-Life-Threatening Conditions* and FDA guidance for industry, *Premarketing Risk Assessment*.

Question 9.3.3.:
Consistent with the FDA's Bioresearch Monitoring (BIMO) Program, Dermira proposes to include, at the time of the NDA submission, tabular listings of site information (Part I), subject-level data line listings by site (Part II) and site level datasets (Part III) for all study sites participating in either of the two Phase 3 efficacy and safety trials, DRM04-HH04 and DRM04-HH05, and the open-label extension trial, DRM04-HH06. A BIMO Reviewer's Guide outlining the locations of these listings in the submission will also be provided. Does FDA agree that the proposed BIMO listings for clinical trials DRM04-HH04, DRM04-HH05, and DRM04-HH06 are sufficient to support NDA submission?

FDA Response:
Your approach is acceptable. Refer to the "Office of Scientific Investigations (OSI) Requests" included at the end of these responses.

Question 9.3.4.:

a. Dermira would like to understand the rationale for the request to provide CRFs and narratives for all discontinuations regardless of the reason, rather than for those who died or did not complete the trial due to an adverse event. Would FDA provide additional background on the more comprehensive request for CRFs and narratives for these trials?

FDA Response:
You propose to provide narratives for all serious adverse events regardless of relationship to the study product, pregnancies, pregnancies, severe AEs, and AEs of special interested (i.e., mydriasis, blurred vision, urinary hesitancy/obstruction/retention). In addition, we request you also provide CRFs and narratives for all discontinuations to evaluate for potential safety issues leading to cessation of the drug product and to make sure that discontinuations and adverse events are appropriately characterized.

b. Dermira has elected to stop the open-label extension trial, DRM04-HH06, early because the trial objectives will be met sooner than anticipated (this trial will provide ICH E3 long-term exposure data for approximately 370 subjects for 6 months and approximately 130 subjects for 12 months). Approximately 117 subjects in this trial will be discontinued early due to the prespecified reason, "Sponsor's Decision." Dermira proposes that no CRFs or narratives be provided for these specific subjects. Does FDA agree?

FDA Response:
No, we do not agree. Data from all exposed subjects should be included in safety analyses. It is not clear from your submission if the 177 subjects were only discontinued due to early termination of the study and we will need to examine whether subjects were individually withdrawn for other reasons.

We also refer you to the response above to question 9.3.2 regarding the adequacy of the safety database.

c. Dermira also asks for clarification of the request to provide narratives for subjects who experience hair discoloration. Since this event has neither occurred in our clinical trials nor would be expected based on the pharmacology of DRM04, it is unclear what this request is based on. Would FDA provide more background for this request?

FDA Response:
If this event has not been observed, this can be noted in the application.

2.5. Clinical Pharmacology

Question 9.4.1.:
Based on results from the maximum-use PK trial, DRM07-HH04, supportive data from ECGs collected in Phase 3 and Phase 2 subjects and the known pharmacology of glycopyrronium, Dermira requests a waiver from the need for a thorough QT/QTc trial. Does FDA agree a waiver is appropriate?

FDA Response:
Your waiver request for a thorough QT/QTc assessment is under review. We will provide you a response at a later date.

Meeting Discussion:
In the interval since transmittal of the draft pre-meeting communication our review has concluded that a thorough QT study will not be required. A formal waiver request should be included in your NDA submission.

Additional Clinical Pharmacology Comments:

- We noted that you excluded data that are more than 3 times of the standard deviation away from the expected mean during your primary analysis of the pharmacokinetic (PK) results. We recommend that you conduct the relative bioavailability analysis by including all data from all subjects.

- In your NDA submission, we recommend that you submit files containing PK data and calculated PK parameters in transport file (.xpt) format.

- You should submit the bioanalytical method validation reports and bioanalytical reports for your PK trials. The bioanalysis of the study plasma samples should be supported by adequate long term storage stability data.

- Clarify whether to-be-marketed formulation was used in your maximal use PK trial. If the to-be-marketed formulation was not used, then additional bridging studies might be needed.

- Submit all drug interaction assessment reports in your NDA.

Meeting Discussion:
The sponsor stated they will include the relative bioavailabilty analysis results for all data in their NDA submission. The sponsor clarified that the to-be-marketed formulation was used in the maximal use PK trial.

3.0 ADMINISTRATIVE INFORMATION

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 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.

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.

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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.

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.				

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.

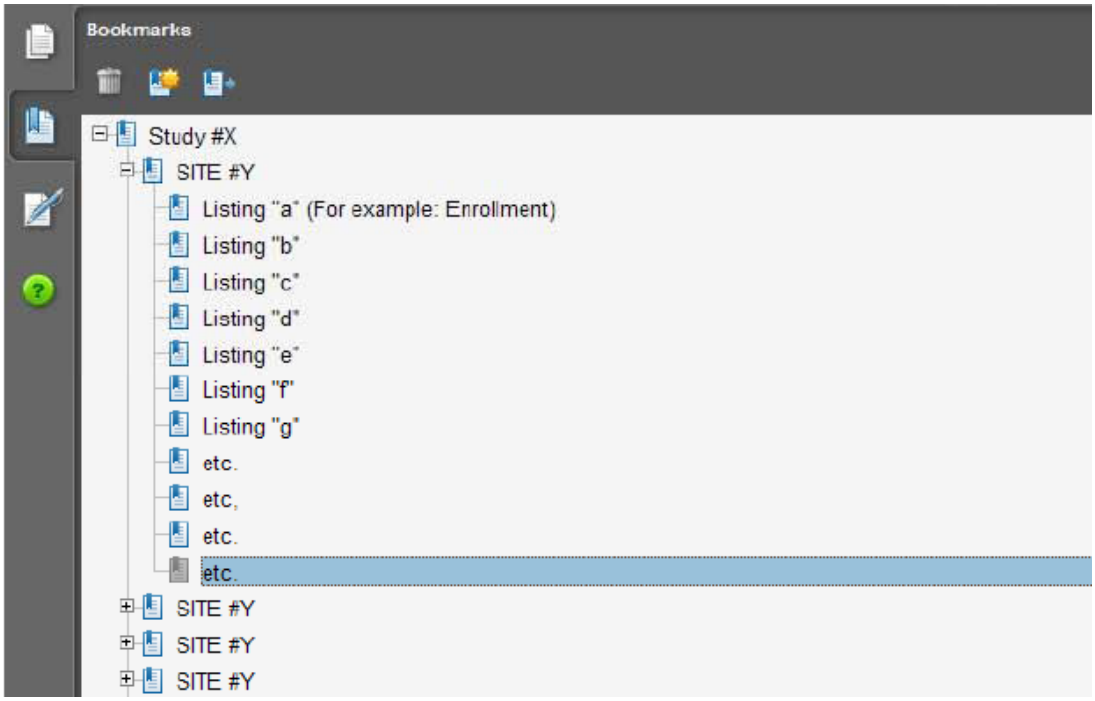
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere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

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

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
02/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104160

MEETING MINUTES

Dermira, Inc.
Attention: Christine Conroy, PharmD
Sr. Vice President, Regulatory Affairs
275 Middlefield Road, Suite 150
Menlo Park, CA 94025

Dear Dr. Conroy:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for glycopyrrolate topical wipes.

We also refer to the meeting between representatives of your firm and the FDA on April 1, 2015. The purpose of the meeting was to discuss the development program for glycopyrrolate topical wipes.

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 Belainesh Robnett, Regulatory Project Manager, at (240) 402-4236.

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:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	April 1, 2015; 8:30 a.m.
Meeting Location:	FDA WO Building 22; Rm. 1315
Application Number:	104160
Product Name:	Glycopyrrolate topical wipes
Proposed Indication:	Treatment of primary axillary hyperhidrosis in adults and adolescents aged 9 to17 years
Sponsor Name:	Dermira, Inc.
Meeting Chair:	David Kettl, MD
Meeting Recorder:	Dawn Williams, BSN

FDA ATTENDEES
Amy Egan, MD, MPH, Deputy Director, Office of Drug Evaluation III (ODE III)
David Kettl, MD, Acting Deputy Director, Division of Dermatology and Dental Products (DDDP)
John Kelsey, DDS, MBA, Dental Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Doanh Tran, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III)
An-Chi Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biopharmaceutics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Yichun Sun, PhD, Quality Assessment Lead, Branch V, Division of New Drug Quality Assessment II (DNDQA II)
Roy Blay, PhD, Good Clinical Practice Assessment Branch, Office of Scientific Investigations (OSI)

SPONSOR ATTENDEES
Eugene A. Bauer, MD, Chief Medical Officer
Janice Drew, MPH Vice President, Clinical & Project Management
(b) (4) Clinical Consultant

(b) (4) PK Consultant
(b) (4) Dermatologist
(b) (4) Biostatistical Consultant
Hans Hofland, PhD, Vice President, Research
Delphine Imbert, PhD, Vice President, Pharmaceutical Sciences
Emily Ip, PhD, Sr. Director, Project Management
Diane Ingolia, PhD, Sr. Director, Regulatory Affairs
Christine Conroy, PharmD, Sr. Vice President, Regulatory Affairs
Luis Peña, Executive Vice President, Product Development
(b) (4) PRO Consultant

Purpose of the Meeting:
Discuss the development program for glycopyrrolate topical wipes

Regulatory Correspondence History

We have had the following teleconferences with you:
- September 11, 2013 Type C (guidance)
- March 23, 2009 Advice/Information Request

We have sent the following correspondences:
- February 4, 2014 Advice
- January 20, 2015 Advice/Information Request
- December 5, 2014 Advice
- August 28, 2014 Special Protocol/Agreement
- August 8, 2014 Advice
- January 3, 2011 Advice
- December 15, 2010 Special Protocol/No Agreement
- May 18, 2009 Advice/Information Request
- March 16, 2009 Information Request

Chemistry, Manufacturing and Controls (CMC)

Question 9.3.1:
Dermira proposes to designate (b) (4) (b) (4) the regulatory starting materials for the production of DRM04 drug substance. Justification for the selection of regulatory starting materials is presented in Appendix 10, Section 1.2. Does FDA agree with the designation of the regulatory starting materials?

Response:
The designation of the starting materials appears reasonable.

Question 9.3.2:
Dermira has developed specifications for the release and stability monitoring of DRM04 drug substance for phase 3 and registration batches as presented in Appendix 10, Section 1.3. The proposed testing criteria were established based on batch history to date and applicable ICH

guidelines. Justification for these specifications is provided in Appendix 10, Section 1.4. Does FDA agree that the proposed drug substance specification is adequate to support phase 3 clinical and registration batches?

Response:
The tests proposed in the drug substance specification appear reasonable to support phase 3 clinical and registration batches of the drug substance. The acceptability of the test methods and acceptance criteria in the drug substance specification will be evaluated during NDA review.

Question 9.3.3:
The proposed DRM04 manufacturing process defines and includes (b) (4) (b) (4) as described in Appendix 10, Section 1.1. Per FDA's advice in a letter dated 09 December 2014, Dermira has developed specifications for both.

Does FDA agree that the proposed specifications (b) (4) as described in Appendix 10, Section 1.5 are adequate to support phase 3 clinical and registration batches?

Response:
The proposed specifications (b) (4) appear reasonable to support phase 3 clinical and registration batches of the drug substance.

Question 9.3.4:
The stability program to support registration of DRM04 Drug Substance will be executed in accordance with FDA/ICH Q1A(R2). Does FDA agree that the proposed stability schedule and scope of testing for the three primary registration batches of DRM04 drug substance as described in Appendix 10, Section 1.7 are adequate to support NDA submission and review?

Response:
The proposed stability program for the drug substance appears reasonable to support NDA submission and review. However, be reminded that the batch size and container closure system of the registration batches of the drug substance should be in line with the ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products*.

Question 9.3.5:
Dermira has developed a drug product specification to control the identity, purity, strength, and quality of the phase 3 clinical and registration lots at release and on stability. The proposed testing criteria were established based on batch history, toxicological qualification, and applicable ICH guidelines. Does FDA agree that the proposed drug product specification for DRM04 Topical Wipes, (b) (4)% (2.4% Glycopyrronium) as described in Appendix 10, Section 2.4 is adequate to support the phase 3 clinical and registration lots?

Response:
The tests proposed in the drug product specification appear reasonable to support phase 3 clinical and registration lots. The acceptability of the test methods and acceptance criteria in the drug product specification will be evaluated during NDA review.

Question 9.3.6:
The stability program to support registration of DRM04 Topical Wipes, (b) (4)% (2.4% Glycopyrronium) will be executed in accordance with FDA/ICH Q1A(R2). phase 3 clinical and registration stability lots will be packaged in the container closure system proposed for the intended, to-be-marketed product. Does FDA agree that the proposed stability schedule and scope of testing provided in Appendix 10, Section 2.8 for the drug product primary registration batches is adequate to support NDA submission and review?

Response:
The proposed stability program for the primary registration batches of the drug product appears reasonable to support NDA submission and review.

Pharmacology/Toxicology

Question 9.2.1:
Does FDA agree that the nonclinical studies completed to date as described in Section 10.5 are sufficient to support conduct of the two proposed phase 3 safety and efficacy trials, DRM04-HH04 and DRM04-HH05?

Response:
The current safety database appears adequate to support conduct of the 4-week clinical trials described under draft protocols DRM04-HH04 and DRM04-HH05, although a final decision concerning the adequacy of the safety database will be made following receipt of the final protocols. Reviewable information concerning the 9-month topical dermal general toxicity study with DRM04 in minipigs ("39-Week Dermal Toxicity and Toxicokinetic Study with DRM04 in Minipigs with a 4-Week Recovery", study No. DRM04-TOX-14-03) should be submitted prior to initiation of the 6 month open-label extension trial (DRM04-HH06). The data should include adequate clinical pathology, histopathology of a full range of tissues, and toxicokinetic analysis. A draft report of the 9-month topical study with minipigs, including attachment of individual animal data and group-mean summary data, with appropriate statistical analysis, should be acceptable to support clinical development under an IND.

Question 9.2.2:
The majority of the nonclinical data supporting an NDA will be based on data owned or generated by Dermira, including a series of oral, parenteral, and dermal toxicology, pharmacokinetic, and genotoxicity studies with glycopyrrolate, as well as additional dermal toxicology studies with DRM04, including an ongoing 2-year dermal carcinogenicity study in rats and an ongoing 9-month dermal toxicology study in minipigs. However, Dermira intends to rely upon FDA's findings of safety for Cuvposa, under the (505(b)(2) regulatory pathway, for certain nonclinical studies, including systemic carcinogenicity and reproductive toxicology studies. Does FDA agree these data are sufficient to support NDA submission?

Response:
In principle, the described approach to addressing nonclinical issues appears to be viable, provided that an acceptable clinical bridge is established between the new product and Cuvposa.

The acceptability of the 9-month topical study with minipigs will be determined during review of that study. If an acceptable clinical bridge is not established to a listed drug(s), then an NDA for the proposed product should be supported by complete nonclinical information, as discussed in the ICH guidance of industry *M3(R2) Nonclinical Safety Studies for the Conduct of Clinical Trials and Marketing Authorization for Pharmaceuticals*. You may not reference information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries of a listed drug for support of safety and/or efficacy of your proposed product. A 505(b)(2) applicant that seeks to rely upon FDA's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug. The adequacy of an NDA submission will be evaluated within the context of CDER's policies that pertain to filing of NDAs.

Clinical/Clinical Pharmacology/Biostatistics

Question 9.1.1:
The proposed phase 3 development plan includes two adequate and well-controlled phase 3 trials, a long-term safety trial, a maximum-use PK trial, and a dermal safety trial. Together with the completed phase 2 trials, data from the phase 3 program will provide a comprehensive data package evaluating DRM04 Topical Wipes in patients with primary axillary hyperhidrosis. Does FDA agree this data package appears reasonable to support submission of an NDA for DRM04 Topical Wipes for treatment of primary axillary hyperhidrosis in adults and adolescents age 9 and above?

Response:
In general, your proposal to conduct two adequate and well-controlled phase 3 trials, a long-term safety trial, a maximum-use PK trial, and dermal safety studies appears to be a reasonable framework for eventual NDA submission. However, Agency feedback regarding the details of the program is further discussed below, as we have comments regarding efficacy endpoints, inconsistent phase 2 study results, size of the safety database, and design of the maximal use trial.

Question 9.1.2:
Two phase 3 trials are planned to confirm the efficacy and safety of DRM04 Topical Wipes, (b) (4) %, in subjects age 9 years and above, with primary axillary hyperhidrosis. The trials, DRM04-HH04 and DRM04-HH05, are randomized, double-blind and vehicle-controlled and will each enroll approximately 330 subjects (total 660 subjects). Subjects will apply study drug daily for 4 weeks.

a. Does FDA agree with the overall design of the two proposed adequate and well- controlled phase 3 safety and efficacy trials?

Response:
The Agency cannot provide agreement on the primary endpoints as noted below. The size of the safety population may not be sufficient to address ICH guideline for industry *E1a The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions*. Additional dose ranging is recommended to

further characterize the performance of your product, and so that treatment estimates for your phase 3 trials can be assessed. See further comments below.

b. A strength of [redacted]% for DRM04 has been proposed for use in phase 3 studies based on data from the dose-ranging study, DRM04-HH01 and additional supporting data from Study DRM04-HH02. As discussed in Section 10.4.1.4, in both studies, active treatment was well-tolerated and efficacy data favored active treatment over vehicle. A dose response was observed in the dose-ranging study, DRM04-HH01, demonstrating improved efficacy with increasing drug strength. Study drug was well-tolerated but also showed that more treatment related adverse events were observed at the highest strength tested (4.0% glycopyrrolate) and that strengths at or below 2.4% w/w glycopyrronium ([redacted]% DRM04 or [redacted]% glycopyrrolate) would be well-tolerated. Does FDA agree with the dose (strength) selected for phase 3 development?

Response:
Based on the safety data reported with the [redacted]% concentration of DRM04, it may be reasonably safe to proceed with this concentration. However, the results of your HH01 and HH02 trials have inconsistencies such that we cannot concur that the optimal dose/concentration has been identified for your phase 3 trials. A consistent dose response relationship has not been identified, and additional dose ranging is recommended.

c. The Sponsor proposes to assess efficacy at the end of a 4-week treatment period using two primary efficacy endpoints and two secondary efficacy endpoints for the phase 3 efficacy and safety studies. The rationale for the selection of these primary and secondary efficacy measures is provided in Section 10.4.2.1.3.3.

The primary efficacy endpoints are proposed as the:

- Mean absolute change from baseline in gravimetrically measured sweat production at Week 4.
- [redacted]

The secondary efficacy endpoints are proposed as the:

- [redacted]
- Proportion of subjects with at least a 50% drop in gravimetrically measured sweat production from baseline to Week 4.

Does FDA agree with the proposed primary and secondary efficacy endpoints?

Response:

No, the Agency does not agree with the selection of the primary endpoints. (b) (4) [redacted]

(b) (4) [redacted]

The Agency again notes that the use (b) (4) [redacted] does not constitute evidence that the measure is well-defined and reliable (b) (4) [redacted] You are again encouraged to develop a reliable, validated, assessment scale which is clinically meaningful and useful for labeling.

The Axillary Sweating Daily Diary (ASDD) is under review by the Agency and comments regarding this scale and its validation will be provided shortly under separate cover. We note, however, your plan to consider this as an exploratory endpoint. Hence, its utility for eventual product labeling will be limited.

You should provide a rationale and supporting evidence that a threshold of 50% decrease drop in gravimetrically measured sweat production from baseline to Week 4 is clinically meaningful. You may wish to investigate higher thresholds, particularly in light of the new phase 2 data submitted in addition to that provided in the briefing document.

d. Does FDA agree with the statistical analyses proposed for the primary and secondary efficacy endpoints, as summarized in Section 10.4.2.1.5?

Response:
Your proposed statistical analysis plan appears generally acceptable, but should be reviewed in light of the Agency comments above regarding your endpoints. However, secondary endpoints intended for labeling should be analyzed with appropriate multiplicity control.

Meeting Discussion:

The sponsor inquired about Agency feedback for their ASDD scale. The Agency noted that the sponsor should receive the feedback regarding the content validity of their ASDD scale shortly, and the Agency committed to providing this advice within 30 days.

There was general discussion regarding endpoints and data from the phase 2 program. Based on feedback from the Agency, the sponsor proposed (b) (4)

There was discussion regarding the threshold of 50% decrease drop in gravimetrically measured sweat production from baseline to Week 4 and whether this was clinically meaningful given the phase 2 study results. The results from the two phase 2 trials were inconsistent and this may impact using this threshold level. Phase 2 trial results may be impacted by the disease severity imbalance at the baseline and result in a high response rate for the vehicle. The threshold level should be determined by the improvement for subjects who achieve success on other scales so that results are consistent across different scales. Achieving statistical significance for an endpoint may not translate to clinically meaningful differences; therefore, the appropriateness of the endpoints should be driven by the clinical relevance.

The Agency encouraged the sponsor to explore further the relevance of their endpoints and get an estimate for their treatment effect to be used for powering the future phase 3 trials.

The sponsor should explore the correlation among the endpoints for subjects achieving success to provide consistency and ensure robustness of findings of the different endpoints.

Question 9.1.3:
The pharmacology of glycopyrronium has been well established. Does FDA agree that based upon the long history of use of intravenous and oral glycopyrronium as noted in FDA's review of Cuvposa, the cardiac safety of glycopyrronium is well characterized, and that no further ECG testing is needed in the phase 3 trials and additionally, that a QT/QTc trial is not required (Section 10.4.2.1.6)?

Response:
Your proposed plan to not conduct a thorough QT/QTc trial appears reasonable provided the maximal use PK trial confirms your expectation that systemic exposure from your product will be less than orally administered Cuvposa. The Agency recommends baseline and periodic on-therapy (Tmax) ECG (single ECG) monitoring in clinical trials to exclude large effects.

Question 9.1.4:
Does FDA agree with the design of the proposed maximum-use pharmacokinetic trial, DRM04-HH07 as discussed in Section 10.4.2.3?

Response:

We recommend that you consider a cross-over study design for Trial DRM04-HH07. The trial should include at least 16 evaluable subjects in the range of 9–17 years of age with sufficient numbers at the lowest ages, i.e., 9 and 10 years of age.

Additional Clinical Pharmacology Comments:
You should address the potential for drug interaction with your product. For further information, refer to the draft guidance for industry *Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*.

Question 9.1.5:
The clinical bridge supporting a 505(b)(2) pathway will use Cuvposa® as the Listed Drug. The bridge will be established by comparing pharmacokinetic data on DRM04 to pharmacokinetic data in subjects dosed orally with Cuvposa. Pharmacokinetic data for DRM04 and for subjects dosed with Cuvposa will be collected as part of the maximum-use pharmacokinetic trial, DRM04-HH07 (Section 10.4.2.3).

Does FDA agree that this approach may be used to establish an adequate clinical bridge for reliance on FDA's findings of safety relative to reproductive toxicology studies, systemic carcinogenicity studies, and information related to the metabolism, elimination and use of glycopyrronium in subjects with renal and hepatic impairment?

Response:
Your approach appears reasonable. The applicability of pharmacokinetic information (e.g., metabolism, elimination, and specific populations) from the listed drug's label to your proposed product will be determined at time of NDA review. Based on the systemic exposure of your product and anticipated systemic adverse effects, you should consider how your product would be labeled with respect to renal impairment, which may cause elevation in systemic drug exposure.

Question 9.1.6:
Does FDA agree with the proposed design of the contact sensitization and cumulative irritation trial, DRM04-HH08 (Section 10.4.2.4)?

Response:
The overall design of the dermal safety studies is acceptable. Evaluation of test sites should include assessment of erythema, edema, and vesiculation. In addition to line listings, results should be reported as both incidence rates (frequency tables) and group means.

Your current proposal for the cumulative irritation study is for "Approximately (b) (4) for Cohort 2 to ensure (b) (4) evaluable subjects." Your numbers should be revised as the Agency typically recommends 35 evaluable subjects.

Question 9.1.7:
DRM04 and DRM04 Topical Wipes do not absorb light above 290 nm. Does FDA agree that photoirritation and photosensitization trials are not required (Section 10.4.2.4)?

Response:
If there is no absorption above 290 nm, phototoxicity and photoallergenicity studies can be waived. Clarify if the provided spectra in Appendix 10, Attachment 2 (page 348) represent testing of the to-be-marketed solution.

Question 9.1.8:
The safety database at the time of NDA submission is anticipated to include exposure data for approximately (b) (4) subjects receiving at least one treatment with glycopyrronium, at any strength, and approximately (b) (4) subjects treated with glycopyrronium, at the intended strength, for 6 months (see Section 10.4.3). Does FDA agree with the size and duration of exposure of the proposed safety database at the time of the NDA submission?

Response:
It does not appear that your proposed development program adequately addresses ICH E1a in terms of size and extent of exposure for assessment of safety. Your product is considered a chronic use product for a non-life threatening condition, and therefore ICH E1a is applicable, which states,

> "Available information suggests that most ADEs first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADEs over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). Usually 300 to 600 patients should be adequate.
>
> There is concern that, although they are likely to be uncommon, some ADEs may increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgment based on the probability of detecting a given ADE frequency level and practical considerations. 100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one-year exposure period this number of patients can provide reasonable assurance that the true cumulative one year incidence is no greater than 3%.
>
> It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500."

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. 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.

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

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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

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 2 (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.

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)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
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.

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
04/20/2015