

MEMORANDUM OF MEETING MINUTES



Meeting Date: March 12, 2007 **Time:** 1:00 P.M.
Location: 1311 **Meeting ID:** 20548
Topic: IND 50,076, 5% Lice Asphyxiator for the Treatment of Head Lice
Subject: Pre-NDA meeting
Regulatory Path: 505(b)(1)
Sponsor: Summers Laboratories, Inc.
Meeting Chair: Stanka Kukich, M.D./Deputy Division Director, DDDP
Meeting Recorder: Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

FDA Attendees:

Stanka Kukich, M.D./Deputy Division Director, DDDP
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP
Patricia Brown, M.D./Clinical Reviewer, DDDP
Barbara Hill, Ph.D./Pharmacology Reviewer, DDDP
Rajiv Agarwal, Ph.D./CMC Reviewer, ONDQA
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDAQ
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII
Clara Kim, Ph.D./Biostatistician, DBIII
Sue-Chih Lee, Ph.D./ Clinical Pharmacology Team Leader, DCPIII
Tien-Mien Chen, Ph.D./Clinical Pharmacology Reviewer, DCPIII
Zei-Pao Huang/Regulatory Information Specialist, OPBS
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Summers Laboratories, Inc.

Ralph D'Agostino, Jr., Ph.D./Statistician, Wake Forest University
Mary Shatzoff, M.S., R.A.C./Regulatory Affairs, Target Health, Inc.
Jules Mitchel, Ph.D./Regulatory Affairs, Target Health, Inc.
Glen Park, Pharm.D./Regulatory Affairs, Target Health, Inc.
Michael Precopio/ President
Colleen Johnson/Toxicology Consultant, Target Health, Inc.
John Colyar, M.B.A./Vice President

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted February 9, 2007) provides background and questions (pp 7-10) for discussion. The sponsor requests input from the Agency on their proposed NDA submission.

Chemistry, Manufacturing and Controls:

Sponsor's Question 1:

Long term stability studies conducted on two batches of drug substance, stored at ambient conditions, for up to 18 months and 24 months, are proposed to support the drug substance in the NDA filing.

Additionally, initial stability data on three batches of drug substance, packaged in a container closure system designed to simulate the commercial system albeit at a smaller scale, and stored according ICH/FDA guidance conditions, will be submitted in the NDA with a commitment to submit updated stability summary reports for these studies as they become available. Does the Agency agree that the proposed long term stability studies are sufficient to support the real time stability data for the drug substance in the NDA?

Agency's Response:

We do not agree. Stability data on samples held at ambient conditions can be used as supporting stability data for the drug substance. Retest dating will be determined primarily based on the stability data generated under the ICH conditions in a container closure system which simulates the commercial system.

The sponsor stated that in the NDA they will propose a ^(c) month retest period for the drug substance.

Sponsor's Question 2:

The sponsor proposes to support the NDA with up to 1 month accelerated stability data (40°C/75% RH) on three batches of the drug substance, packaged in a container closure system which simulated (b) (4) A commitment to submit updated stability summary reports for these stability studies will be provided in the NDA. Does the Agency agree that the proposed accelerated stability studies are sufficient to support the drug substance in the NDA?

Agency's Response:

Submission of only 1 month of accelerated stability data in the NDA would be acceptable, but the actual retest dating will be determined based on the stability data submitted in the NDA and primarily based on the data generated under the ICH conditions and in a container closure system which simulates the commercial system. We do not guarantee the review of a stability amendment during the review cycle.

Additional Comments:

1. Please provide samples for the evaluation of the proposed dosage form nomenclature, lotion/ (b) (4) The samples should cover the lower and upper limits of the proposed viscosity specification.

The Agency referred the sponsor to CDER Standards Manual for current Agency thinking on dosage form nomenclature.

2. Please clarify the function of mineral oil in the formulation.

The sponsor clarified that the role of the mineral oil is (b) (4)

3. We recommend that you control the amount of benzene in the drug product by controlling the amount of benzene in (b) (4) the excipient (b) (4). Carbopol 934P is not benzene free. We recommend that you investigate the use of (b) (4) (b) (4) Using the scientific principles outlined in our SUPAC-SS guidance, for this change (b) (4)

The Agency requested that the sponsor (b) (4) the drug product specification.

4. The acceptance criterion of benzene (b) (4) This limit is allowed under ICH Q3C, however considering the use of this product in the pediatric population, we recommend that you reduce the amount of benzene (b) (4)

Pharmacology/Toxicology:

Sponsor's Question 3:

The Sponsor has completed nonclinical studies to support the NDA and does not plan to conduct any additional nonclinical studies. Does the Agency agree with this plan?

Agency's Response:

Yes. The sponsor's proposal is acceptable from a Pharmacology/Toxicology perspective.

Clinical Pharmacology

Sponsor's Clinical Pharmacology Question:

"A request for waiver of human bioavailability study was submitted as Serial 015 on 8/30/05. A formal response was not received from the Agency. The request for waiver of human bioavailability study was based on the following:

"The Division has indicated that the Sponsor either needs to provide (1) evidence demonstrating that in vivo bioavailability of the drug product... or (2) provide information to permit the FDA to waive the submission of evidence demonstrating in vivo bioavailability." Exposure data have been collected from the 14-day repeat-dose dermal toxicity studies performed in rats and dogs using the drug product at the clinical and enhanced concentrations. Summaries of these studies conducted by the sponsor [were] provided and the referenced studies were submitted in the original IND.

Summers believes that these data support the request to waive the requirement for a bioavailability study in humans. Does the Agency agree with this proposal?

Agency's Comment:

No. The animal study will not suffice as the evidence to permit a biowaiver. An in vivo bioavailability study in humans is necessary to address the following:

The systemic exposure for the final to-be-marketed formulation of the proposed Lice Asphyxiator (Benzyl Alcohol 5%) product in the US under maximal usage conditions in a suitable number of (evaluable) patients of different age ranges (6 months to 3 years, 4 years to 11 years, and 12 years and older) with the disease of interest at the upper range of severity as anticipated in the clinical trials.

Such a trial would attempt to maximize the potential for drug absorption to occur by incorporating the following design elements:

- a) Frequency of dosing
- b) Duration of dosing
- c) Use of highest proposed strength
- d) Total involved surface area to be treated at one time
- e) Amount applied per square centimeter
- f) Method of application/site preparation

In addition, the assay method should be sensitive for the purpose.

The sponsor presented their rationale for the biowaiver request which is attached to the minutes. The request for the study may affect the timing of their NDA submission. The Agency will have an internal discussion and provide a response as soon as possible.

Addendum to CP Comments:

The Agency acknowledges the sponsor's request for a biowaiver. However, after further discussion with the Clinical Pharmacology Group, including the Division Director, Dr. Dennis Bashaw, we have determined that a biowaiver cannot be granted. A complete protocol for the pharmacokinetic (PK) study in patients should be submitted to the Agency for review no later than 2 months after receipt of these meeting minutes. Our review comments if any will be conveyed to you as soon as possible. This PK study should be initiated no later than 4 months after receipt of the meeting minutes.

We reiterate that the above PK study should be conducted in target population with an appropriate number of (evaluable) patients in different age groups, i.e., 6 months to 3 years, 4 years to 11 years, and 12 years and above.

Clinical and Biostatistics

Sponsor's Question 4:

The Statistical Analysis Plan for Protocol No. SU-01-2005 was submitted to the Division (Serial 0027). A brief report (excluding some appendices) of the effectiveness and safety results for this study are submitted in the briefing document for this meeting. Does the Agency agree that the data analysis and presentation are appropriate for their review?

Agency's Response:

Yes. The data analysis in the brief report appears to follow the Statistical Analysis Plan and seems to be appropriate for review.

Sponsor's Question 5:

The sponsor does not plan to pool the results of the double-blind, pivotal studies in the Integrated Summary of Effectiveness but to present side by side displays of the results. Does the Agency agree with this plan?

Agency's Response:

Yes.

Sponsor's Question 6:

The sponsor plans to include the Integrated Summary of Effectiveness and the Integrated Summary of Safety in Module 2 of the eCTD and provide a reference to this section in Module 5. Does the Agency agree with this plan?

Agency's Response:

No, the ISS and ISE should be included in module 5 (with a reference to this section in Module 2), and should include comprehensive and full evaluations of safety and efficacy of the proposed drug product. The summary can be included in module 2.

Sponsor's Question 7:

The sponsor plans to present safety results overall and by the following age groups: 6 months to 3 years, 4 years to 11 years, and 12 years and older. Does the Agency agree with this plan?