

Agency's Response:

This is acceptable.

Sponsor's Question 8:

Summers Laboratories, Inc. intends to submit an application for Lice Asphyxiator (benzyl alcohol), 5% Lotion in eCTD format. The electronic submission will be prepared in accordance with the ICH eCTD Specifications, version 3.2, dated February 04, 2004, and the following current FDA Specifications/Guidance:

- eCTD Backbone Files Specification for Module 1
- eCTD Backbone Files Specification for Modules 2 through 5
- eCTD Backbone Files Specifications for Study Tagging Files
- eCTD Table of Contents Headings and Hierarchy
- Study Data Specifications
- SPL Schema for Implementation

Does the FDA agree that the proposal to submit the NDA in the eCTD format will be acceptable?

Agency's Response:

The electronic submission is acceptable to the agency. Please refer to the following website to find the most current version of the eCTD specifications.

<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

Sponsor's Question 9:

Summers Laboratories, Inc. requests a waiver for providing an eCTD sample submission because (b) (4) will be compiling the eCTD. (b) (4) filed an acceptable eCTD pilot with the Center on June 2004 (Ref: Pilot number 900024). Does the Agency agree that the eCTD sample submission can be waived?

Agency's Response:

Yes, the (b) (4) consultant has obtained an acceptable sample eCTD from the agency so the waiver is granted.

Sponsor's Question 10:

Summers Laboratories, Inc. is planning to submit a full eCTD submission as the archival copy. The only paper copies that will be provided with the archival copy will be for those items with original signature (cover letter, Form FDA 356h, patent information, patent certification, debarment certification, field copy certification, user fee cover sheet and financial disclosure). These documents will be submitted electronically as well. The eCTD will be provided in accordance with all the above referenced specifications and guidance (please see Question 8).

All documents will be bookmarked and hyperlinked in accordance with the 1999 FDA guidance, "Providing Regulatory Submissions in Electronic Format – General Considerations," and "Providing Regulatory Submissions in Electronic Format – NDAs."

The following is a discussion of the sections of the eCTD that require specific electronic formats and/or organization:

Labeling

The proposed labeling text will be submitted in SPL format, and it will be in accordance with the FDA current SPL schema. The proposed labeling will also be provided in Microsoft WORD format. All additional labeling components (e.g. carton, containers, etc.) will be provided as PDF files.

Agency's Response:

The labeling formats as proposed are acceptable.

Case Report Tabulation

SAS datasets will be provided in lieu of case report tabulations in accordance with the 1999 FDA guidance, "Providing Regulatory Submission in Electronic Format – General Considerations," and "Providing Regulatory Submissions in Electronic Format – NDAs." Each dataset will be provided as a SAS transport file in accordance with the above referenced guidance. Both raw and analysis datasets will be provided.

Agency's Response:

Please follow the "Study Data Specification" guidance for creating folder structure and transport file. The guidance can be located at the following website:
<http://www.fda.gov/cder/regulatory/ersr/ectd.htm>

Case Report Forms

Case report forms will be submitted for any patients who died or discontinued due to an adverse event. Each case report form will be submitted as a single PDF file and will be bookmarked by visit and domain. Does the Agency agree with the proposed electronic formats and organization of the eCTD submission?

Agency's Response:

Case Report Forms (CRFs) should be submitted from the pivotal studies for:

- a) all Serious AEs
- b) all Severe AEs
- c) all patients who discontinued for whatever the reason (not just because of adverse events)

Please submit narrative summaries for:

- a) deaths
- b) dropouts
- c) serious AEs

Guidelines for narrative summary content are provided on page 26 of the Guidance for Industry- Pre-marketing Risk Assessment – <http://www.fda.gov/cder/guidance/6357fnl.pdf>

Sponsor’s Question 11:

If approved, Lice Asphyxiator, 5% (b) (4) would represent a significant improvement compared to marketed products from a benefit risk perspective in the treatment of head lice. Currently approved pesticide pediculicides are [*sic*] have reduced effectiveness due to developed resistance and have serious safety risks when not used properly. Therefore, the sponsor believes that Lice Asphyxiator, 5% (b) (4) is eligible for priority review. Does the Agency agree that the Lice Asphyxiator, 5% (b) (4) is eligible for priority review?

Agency’s Response:

Drug products may qualify for priority review through demonstration of: “... (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.” (CDER Manual of Policies and Procedures 6020.3) If the sponsor believes that their product qualifies for priority review, they are encouraged to present their case with the NDA submission.

Additional Clinical and Biostatistics Comments:

1. Please ensure that the adverse event (AE) data set contains the following:
 - a) Full MedDRA Hierarchy
 - b) Primary and secondary SOCs
 - c) All data in same version of MedDRA
2. Please submit the coding dictionary, consisting of a list of all investigator verbatim terms and the preferred terms to which they were mapped, with the NDA. It is most helpful if this comes as a SAS transport file.
3. The sponsor should provide their planned pooling strategy for the Integrated Summary of Safety. Individual study reports should be provided.
4. Please include the full text version of any referenced articles.
5. The Agency recommends the sponsor to submit the data based on the Study Data Tabulation Model (SDTM). Questions about SDTM can be sent to Cder-edata@cder.fda.gov. If the sponsor prefers not to follow SDTM, please consider the following when submitting the data. The sponsor should provide the Agency with SAS transport files in electronic form. The data sets should include demographic and baseline data as well as efficacy and safety data. Data Sets should include:
 - a. The database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.

- b. Each data set should include the treatment assignments. For each of the primary and secondary endpoints, an indicator variable that denotes whether measurements are actual or imputed should be included.
- c. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.
- d. In addition to the electronic data sets, the NDA submission should include the following items:
 - o Study protocols including the statistical analysis plan, protocol amendments and their dates, and a copy of the Case Report Form.
 - o The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Administrative Comments

1. 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).
2. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
3. All manufacturing facilities named in your application should be ready for inspection when the application is submitted. We recommend that this information be provided in the application in the form of a table or spread sheet so that these sites can be properly identified early in the review process.
4. The sponsor is reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
5. The sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.
6. We note that SPL should be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); Guidance for Industry: *Providing Regulatory Submissions in Electronic Format — Content of Labeling* (April 2005); <http://www.fda.gov/ohrms/dockets/dockets/92s0251/92s-0251-m000032-vol1.pdf>], you are required to submit to FDA prescribing and product information (i.e., the package insert or label) in SPL format. During the initial implementation phase of the PLR (until the end of 2006), FDA advises applicants to make a good faith effort to provide PLR-compliant SPL with their marketing applications or efficacy supplements. FDA will work closely with applicants during the review

cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Please submit the completed Highlights Data Element Table. To complete the Highlights data elements, please refer to the following two documents at the FDA Data Standards Council website (<http://www.fda.gov/oc/datacouncil>) under Structured Product Labeling: "Companion Document for SPL Release 2 Implementation Guide for Highlights DRAFT" and "SPL Highlights Data Element Table." The companion document provides information on the appropriate terminology standards. If you need assistance completing the Highlights data elements portion of your application, please contact spl@fda.hhs.gov. Structured Product Labeling (SPL):

The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

Minutes Preparer: _____
Melinda Bauerlien, M.S./Regulatory Project Manager, DDDP

Chair Concurrence: _____
Stanka Kukich, M.D./Deputy Division Director, DDDP

Sponsor's Handout

The issue of a biowaiver based on animal TK data was first raised at the end of phase 2 meeting, September 9, 2004.

At the Type A Meeting held August 8, 2005 we discussed safety monitoring in the Phase III clinical studies. In response to the discussion about the need to monitor clinical laboratory in the Phase III studies the issue of a biowaiver was again raised. Based on the discussion at the meeting and prior to initiation of the studies, we submitted the original biowaiver request August 30, 2005. We believed that because the Agency permitted conduct of the Phase III studies in children 6 months of age and older without monitoring for systemic effects, the biowaiver issue had been resolved.

Based on 21CFR 320.22, it is our opinion that a biowaiver is possible on the basis that LA 5% is a topical product that contains benzyl alcohol at the same or lower concentration as is found in currently approved products that contain benzyl alcohol as an inactive ingredient (e.g., benzyl alcohol 50% in a topical gel). In addition, there are numerous other injectable, oral and topical approved products with benzyl alcohol listed as an inactive ingredient at concentrations higher than LA 5% (e.g., IM injection 10%).

We provided the animal studies as supportive data with regard to relative exposure. Based on 21CFR 320.24(b)(1)(iii), we provided an in vivo animal model with toxicokinetic data to support the biowaiver. The animal models used are standard models for assessing exposure. In these studies, the exaggerated exposure (both concentration and duration of exposure) achieved in the animal studies resulted in low plasma levels only at 1 hour post dose. In addition, in human use, the vast majority of the product is applied to the hair and not the scalp and for only 10 minutes. There were also no safety concerns in the animal studies under these exaggerated conditions and there have been no safety concerns in the human studies.

As presented in 21CFR 320.25(a)(1) and (a)(2), we also have concerns about doing unnecessary research in humans to address this issue, not only in adults, but particularly in children as young as 6 months of age, when we have provided a valid animal model. We do not believe that the risk to benefit is justified for the proposed use of the product.

(a)(1) "The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done."

(a)(2) "An in vivo bioavailability study shall not be conducted in humans if an appropriate animal model exists and correlation of results in animals and humans has been demonstrated."

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/s/

Stanka Kukich
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