CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-501

MEDICAL REVIEW(S)

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products

Date: October 2, 2006

From: Susan Johnson, Ph.D.
Associate Director

To: NDA 21-501/N-000
L'Oreal Products, Inc.
Vichy Capital Soleil 15
Lancome UV Expert 15

Subject: NDA Approval

This sunscreen product contains avobenzone 2%, ecamsule 3% and octocrylene 10% in a water resistant lotion formulation. Avobenzone and octocrylene have been marketed for many years in combination under the OTC monograph. Ecamsule was a new molecular entity, recently approved in NDA 21-502, an SP 15 sunscreen lotion combination of the same ingredients from L'Oreal.

The efficacy reviews by Michael Koenig, interdisciplinary scientist in the ONP Division of Nonprescription Regulation Development, found that the formulation meets the criteria for UVB radiation protection at an SPF 15 level and also protects against UVA radiation such that it may claim "broad spectrum" protection as an indication. Safety assessments were conducted by Daiva Shetty in the ONP Division of Nonprescription Clinical Evaluation. Based on the pharmacology/toxicology by Jiaquin Yoa, mo preclinical data were suggestive of clinical safety concerns. Adverse events from application of the combination were minimal, with no serious safety effects reported. Clinical pharmacology assessments from Dennis Bashaw found minimal systemic exposure that is unlikely to have clinical relevance. The deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA), for children less than 6 months of age, is considered a required postmarketing study commitment and the final report submission is due July 22, 2009. The chemistry review by Sue-Ching Lin and product microbiology review by Stephen Langille support product approval. There are no ingredients in this formulation that were manufactured [redacted] b(4)

It is recommended that NDA 21-501 be approved for use on adults and children ages 6 months and older.

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/s/

Susan Johnson
10/2/2006 02:39:56 PM
UNKNOWN

MEDICAL REVIEW (DERMATOLOGY)
NDA 21-501 and 21-502
— SPF 15 Water Resistant Sunscreen Cream
— SPF 15 Daily Use Moisturizer Sunscreen Cream

b(4)

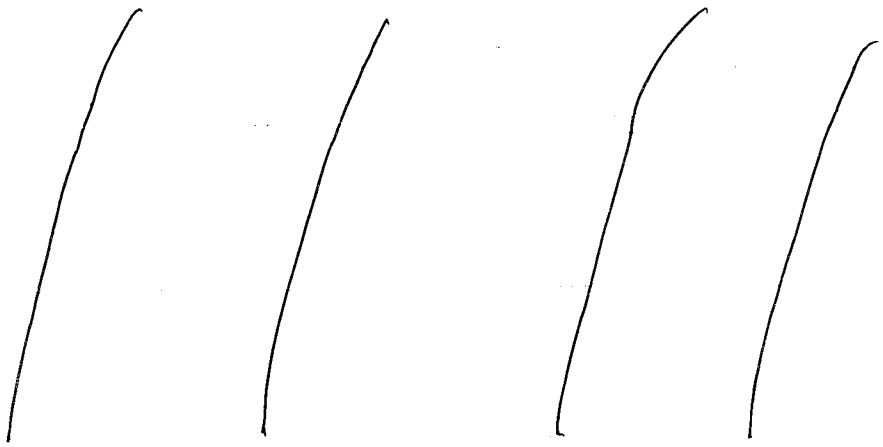
June 29, 2006

L'Oreal USA Products, Inc., the applicant for these two NDA products has submitted a complete response to the prior Approvable letters for the respective NDAs dated March 10, 2006.

No new information was submitted regarding the efficacy of the drug products. However, revised labeling is submitted. The labeling considerations were the primary reason for not approving these products during the prior review cycle. Several claims requested by the sponsor were unsubstantiated in the information submitted to the Agency. In addition, a safety update is submitted, which is the subject of review by Drs. Shetty and Feibus in the Division of Nonprescription Clinical Evaluation (dated 6/7/2006).

For relevant review of efficacy, please refer to prior reviews by Dr. Phyllis Huene, Medical Officer, Dermatology, which recommend approval of these sunscreen products from the standpoint that sufficient efficacy has been demonstrated. Please also refer to the reviews of the SPF and UVA studies by Mr. Koenig of the non-prescription drug review division.

The labeling claims were reviewed upon resubmission by Mr. Koenig and the clinical team and the following items were communicated with the sponsor in the Discipline Review letter dated June 13, 2006:



b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

It is the recommendation of the reviewing dermatologist that this product be approved with labeling that is appropriate and substantiated, which will include addressing the ten items listed above that have been conveyed to the sponsor.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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/s/

Markham Luke
6/29/2006 08:21:13 AM
MEDICAL OFFICER

Labeling review to be done by Non-Prescription drugs in collaboration with DDDP.

Susan Walker
7/10/2006 08:14:23 PM
DIRECTOR

MEDICAL OFFICER REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

NDA #:	21-501 & 21-502
Drug name:	[redacted] SPF 15 W/R Sunscreen Cream b(4) [redacted] SPF 15 Daily Use Moisturizer Sunscreen Cream
Sponsor:	L'Oreal USA Products, Inc.
Pharmacologic Category:	Sunscreen
Proposed Indications:	Prevention of sunburn [redacted] due to sun exposure b(4)
Dosage Form:	Cream
Route of Administration:	Topical
Submission Date:	May 18, 2006
Review Date:	June 3, 2006
Reviewer:	Daiva Shetty, MD

Introduction:
This is a clinical review of the safety update for two combination sunscreen drug products submitted under two different NDAs, 21-501 and 21-502.

NDAs 21-501 and 21-502 were originally submitted by L'Oreal USA Products, Inc in May of 2005. Both of the NDAs have been reviewed by FDA and were assessed as approvable because of deficiencies in labeling and delayed manufacturing facility inspection. The current submission is the sponsor's response to the 3/10/2006 Approvable Letter. It includes new proposed labeling and a safety update.

For detailed review of the two sunscreen drug products refer to the original medical officer reviews. This review addresses only the safety update portion of the submission. Since the clinical data to support the marketing of both the products are the same, the two NDAs will be reviewed together. An interdisciplinary scientist in the Division of Nonprescription Regulation Development is reviewing formatting and content changes to the re-proposed labeling.

Background:
NDA 21-501 is for the — SPF 15 water resistant (W/R) sunscreen cream. — b(4)
SPF 15 W/R cream is a topical combination sunscreen composed of the following three active sunscreen ingredients:

- Avobenzone 2%
- Octocrylene 10%
- Ecamsule (Mexoryl®) 3%

The sponsor is requesting to market this formulation under five different brand names:

1. UV EXPERT 15
2. ———————
3. ANTHELIOS 15 b(4)
4. ———————
5. CAPITAL SOLEIL 15

b(4)

NDA 21-502 is for the — SPF 15 Daily Use Moisturizer Sunscreen Cream. —
SPF 15 cream is a topical combination sunscreen composed of the following three active sunscreen ingredients:

- Avobenzone 2%
- Octocrylene 10%
- Ecamsule (Mexoryl®) 2%

The sponsor is requesting to market this formulation under six different brand names:

1. UV PROTECTIVE —
2. UV ACTIV
3. ANTHELIOS SX b(4)
4. UV EXPERT 15
5. ———————
6. UV DEFENDER

The sponsor is proposing to market both of the combination sunscreen products in the OTC setting for daily use in children six months of age and older and in adults in accordance with all requirements of the existing OTC sunscreen product regulations, 21 CFR Part 352.

Safety Update Review:
The Safety Update consists of the latest safety information collected by L'Oreal for their ecamsule-containing sunscreen products through year end 2004. This information has been compared to previous information reported in NDAs 21-501 and 21-502 through 2002 and the additional information submitted in the 120 day Safety Update Report on September 9, 2005.

The sponsor states that no additional non-clinical or clinical data have been generated with — formulations or with ecamsule since the original submission of the two NDAs. Safety information in this submission comes from two sources: L'Oreal's postmarketing cosmetovigilance database and literature. b(4)

Results of the literature search since the update reported September 8, 2005 through March, 2006, consist of one article.[1] The article reported two cases of contact dermatitis in 3- and 10-year-old children, following application of sunscreen products containing 10% octocrylene. Both children underwent contact allergy testing and were found to be allergic to the octocrylene component of the sunscreens. Severity and outcomes of the cases were not reported in the article.

Comment:
Contact sensitivity to a topically applied sunscreen products is not an unusual adverse reaction. Labeling for both of the sunscreens under this review already carry a warning to stop use the product if rash or irritation develops or lasts.

L'Oreal Postmarketing Pharmacovigilance/Cosmetovigilance Data Review

The original submission covered cosmetovigilance information received for the period through year end 2002 and the 120 day Safety Update of September 8, 2005 reported information through 2003. This update contains postmarketing adverse event data through 2004 with a special focus on adverse events reported between 2003 and 2004.

b(4)

From 2003 through year end 2004, more thar [redacted] camsule or [redacted] solution have been produced. Approximately [redacted] countries where the cosmetovigilance system is in place through 2004.

For all reported spontaneous adverse reactions, a conservative estimate of 54 adverse events per million units sold of all ecamsule-containing product formulations has been reported during 12 years of marketing through 2004, an overall adverse event incidence of 0.0054% (derived from a total of [redacted] pontaneous adverse events reported during the same time period and [redacted] nits sold). The incidence of adverse reports is relatively stable over time.

(4)

In the database, there are a total of 3837 spontaneous adverse event reports in children reported through 2004. The database defines children as individuals 16 years of age and younger. Over an 11-year period, the incidence of adverse events among children is 0.0142% with 14 adverse events per million units sold. It is assumed that most reactions occurred while using children's products.

Summary of incidence of adverse events associated with use of ecamsule-containing products for children and all subjects presented in Table 1 below.

[1] Madan V and Beck MH. Contact allergy to octocrylene in a sunscreen with recurrence from passive transfer of cosmetic. Contact Dermatitis 2005;53:2141-42.

Table 1. Summary of Incidence of AEs Associated with Use of Ecamsule-Containing Products for Children and for all Subjects

Adverse Event Term	Incidence of all AEs per million units sold 1993-2004*	Incidence of children's AEs per million units sold 1993-2004**
	Number of AEs and % of units sold for each subgroup	
All adverse events	54.4 (0.0054)	142 (0.142)
Erythema	11.9 (0.0012)	38.9 (0.0040)
Dermatitis	10.3 (0.0010)	35.6 (0.0036)
Skin Discomfort	7.8 (0.00078)	9.5 (0.0010)
Pruritus	6.5 (0.00065)	18.4 (0.0018)
Edema Skin	4.7 (0.00047)	16.6 (0.0017)
Irritation	3.5 (0.00035)	5.2 (0.00052)
Dry Skin	1.9 (0.00019)	4.3 (0.00043)
Desquamation	1.3 (0.00013)	1.1 (0.00011)
Eczema	1.3 (0.00013)	2.5 (0.00025)
Allergic Local Reaction	0.92 (0.00009)	0.96 (0.00010)
Conjunctivitis	0.98 (0.00010)	0.78 (0.00008)
Photosensitivity	0.56 (0.00006)	0.52 (0.00005)
Lacrimation Disorder	0.59 (0.00006)	0.74 (0.00007)
Skin Burn	0.61 (0.00006)	1.6 (0.00016)
Sunburn	0.34 (0.00003)	1.3 (0.00013)
Urticaria	0.30 (0.00003)	2.1 (0.00021)
Skin Discoloration	0.20 (0.00002)	0.37 (0.00004)
Acne	0.21 (0.00002)	0.04 (0.000004)
Edema Coniunctival	0.16 (0.00002)	0.81 (0.00008)

b(4)

Table 2 lists the frequency of adverse events in descending order as a percentage of all adverse reactions reported for two groups – children and adults > 16 years of age for the specific year 2004 and for the time period 1993 through 2003 for comparison.

Table 2. Summary of AEs as % of All Terms in Descending Order Associated with Use of Ecamsule-Containing Products: Frequency of AEs > 0.2%

Adverse Event Term	Frequency of AEs as % of all AEs in adults for the year 2004	Frequency of AEs as % of all AEs in adults for years 1993-2003	Frequency of AEs as % of all AEs in children for the year 2004	Frequency of AEs as % of all AEs in children for years 1993-2003
	Number of Adverse events as % of all adverse events in each subgroup			
All adverse events	**100%**	**100%**	**100%**	**100%**
Erythema	25.20	20.50	31.30	27.00
Dermatitis	13.00	18.30	24.70	25.10
Skin discomfort	14.80	15.30	3.80	7.00
Pruritus	10.00	11.90	10.70	13.20
Edema skin	9.40	7.90	12.50	11.60
Irritation	6.40	7.20	6.60	3.30
Dry skin	3.70	3.70	3.00	3.00
Desquamation	2.70	2.70	0.00	0.84
Eczema	1.80	2.60	1.80	1.70
Allergic local reaction	0.57	2.10	0.00	0.75
Conjunctivitis	4.30	1.90	1.00	0.49
Photosensitivity	0.40	1.30	0.25	0.38
Lacrimation disorder	2.40	1.10	1.30	0.44
Skin burn	2.30	0.92	1.00	1.10
Sunburn	0.34	0.59	0.76	0.93
Urticaria	0.17	0.36	0.51	1.60
Skin discoloration	0.28	0.39	0.25	0.26
Acne	1.30	0.39	0.00	0.03
Edema conjunctival	0.45	0.21	0.00	0.64
Eye pain	0.28	0.08	0.00	0.06

The sponsor states that for the year 2004, there were no serious adverse events reported into the cosmetovigilance database. Serious adverse events reported prior to 2004, were discussed in the NDA 21-501 and 21-502 safety review.

Conclusions:
The updated postmarketing data for ecamsule-containing sunscreen drug products did not reveal new serious adverse events. The safety profile of these sunscreens is consistent with that from previous years. Most frequently reported adverse events were local application skin reactions (erythema, dermatitis, pruritus, edema, dry skin, skin irritation, etc.) or signs of eye irritation. The incidences of these reactions were not significantly different in children compared to adults.

The proposed — SPF 15 W/R Sunscreen Cream and — SPF 15 Daily Use Moisturizer Sunscreen Cream have an acceptable safety profile for over-the-counter marketing. b(4)

Recommendation:
Based of the safety profile — SPF 15 W/R Sunscreen Cream and — SPF 15 Daily Use Moisturizer Sunscreen Cream should be approved for over-the-counter marketing. b(4)

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/s/

Daiva Shetty
6/7/2006 09:15:33 AM
MEDICAL OFFICER

Karen Feibus
6/12/2006 01:12:11 PM
MEDICAL OFFICER

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: **March 6, 2006**

From: **Andrea Leonard-Segal, M.D.**
Acting Director

Subject: **NDA 21-501 — SPF 15 Water Resistant (W/R) Sunscreen Lotion [ecamsule (Mexoryl®) 3%; avobenzone 2%; octocrylene 10%]**

NDA 21-502 — SPF 15 Sunscreen Daily Lotion [ecamsule 2% (Mexoryl®); avobenzone 2%; octocrylene 10%]

NDA 21-471 — SPF 20 W/R Sunscreen Lotion [ecamsule 2% (Mexoryl®); avobenzone 2%; octocrylene 10%; titanium dioxide 2%]

Sponsor: **L'Oreal USA Products, Inc.**

RECOMMENDATIONS:
NDA 21-501 and NDA 21-502 should be approved if:

- the chemistry inspection is completed and the site is found to be acceptable before the PDUFA date
- the labeling is revised before the PDUFA date in accordance with the FDA comments sent by FAX to the sponsor

Otherwise the sponsor should receive an approvable letter.

As a Phase 4 commitment to address the Pediatric Research Equity Act, the sponsor should be asked to perform safety and pharmacokinetics studies in babies < 6 months of age.

The chemistry and labeling reviews and the Division of Scientific Investigation inspection for NDA 21-471 are pending and will be considered in a follow-up division director memorandum.

BACKGROUND:

L'Oreal is seeking approval for the nonprescription marketing of three —— sunscreen drug products for daily use by adults and children at least 6 months of age. The sponsor states that the three products are indicated "for the prevention of sunburn —— —› ollowing — exposure to ultraviolet radiation." This indication includes both an ultraviolet (UV) B and a UVA radiation protection claim. The UVB claim is "helps prevent sunburn/protects against UVB radiation." This UVB claim is allowed for nonprescription sunscreens marketed under the monograph system (21 CFR 352.52(b)(1). A UVA claim is under development via the nonprescription ingredient rulemaking process; a tentative final monograph (TFM) and amendments to it have been published addressing UVA claims and testing methodology.

The sponsor has developed the combination of active ingredients in these sunscreen products in an attempt to provide a product that absorbs UV radiation across a relatively broad range of the spectrum.

- New Drug Application (NDA) 21-501 is a sun protection factor (SPF) 15 water resistant sunscreen lotion
  (ecamsule 3%; avobenzone 2%; octocrylene 10%)

The sponsor plans to market this formulation in tubes and requests that this formulation be marketed under five different brand names. (See page 8 of Dr. Michael Koenig's efficacy review.)

- NDA 21-502 is a SPF 15 sunscreen lotion
  (ecamsule 2%; avobenzone 2%; octocrylene 10%)

The sponsor requests that this formulation be marketed under seven brand names. The sponsor intends to market this formulation in tubes and also in pump bottles. (See page 8 of Dr. Michael Koenig's efficacy review.)

- NDA 21-471 is a SPF 20 water resistant sunscreen lotion
  (ecamsule 2%; avobenzone 2%; octocrylene 10%; titanium dioxide 2%)

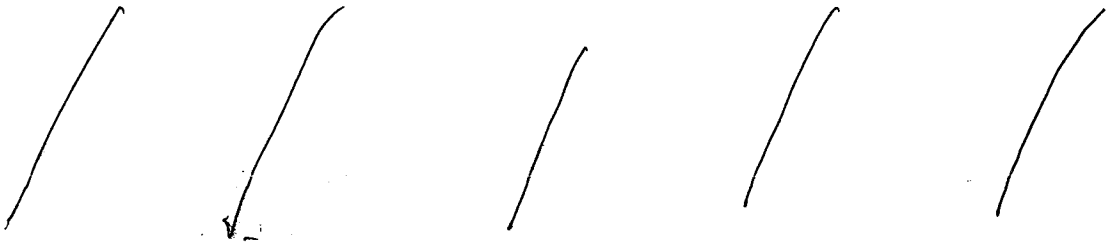
The sponsor requests that this formulation be marketed under four brand names and plans to market it in tubes. (See page 8 of Dr. Michael Koenig's efficacy review.)

The clinical data to support the marketing of the three products are the same, so the three NDAs have been evaluated concurrently by the reviewers and will be treated similarly in this division director memorandum. Each of these three products contains ecamsule, an active ingredient that has been marketed since 1993 in Europe where the allowed concentration range of ecamsule is up to 10%. Ecamsule has also been approved since 1994 in Canada, and since 1995 in Australia. Ecamsule is a new molecular entity in the United States.

The other active ingredients in these sunscreens (avobenzone, octocrylene, and titanium dioxide) are among the 16 generally recognized as safe and effective sunscreen active ingredients listed in the over-the-counter (OTC) drug sunscreen drug monograph (21 CFR 352). The concentrations of the avobenzone, octocrylene and titanium dioxide in the L'Oreal products are concentrations that the monograph allows. The sunscreen

monograph was finalized on May 21, 1999 and did not include the combination of avobenzone with titanium dioxide as an acceptable combination of active ingredients because data demonstrating the combination is effective was lacking. However, FDA issued a stay of the effective date on Dec. 31, 2001. The effective date is stayed until FDA publishes the UVA testing and labeling components of the monograph.

The sponsor opened IND 59,126 on October 15, 1999 to study the three [redacted] sunscreen formulations. The pharmacology/toxicology section of this IND submission contained studies that had been reviewed under [redacted] b(4)



DISCUSSION:

Chemistry:

See the reviews by Dr. Sue-Ching Lin for NDA 21-501 and for NDA 21-502. For both NDAs Dr. Lin recommends that, if the inspection at the [redacted] acility is acceptable, the applications could be approved from a chemistry standpoint. [redacted] is one of the avobenzone drug substance manufacturing sites and the inspection is pending as of the date of the Division Director Memo. The NDA cannot be approved without an "acceptable" recommendation from the Office of Compliance for all the manufacturing and control facilities. b(4)

There were many communications between the Agency and the sponsor regarding whether the dosage forms for the two NDA products are creams or lotions. During the February 10, 2006 telephone conference FDA informed the applicant that the two NDA products are creams, instead of lotions as proposed by the sponsor in their labeling for the three [redacted] products. b(4)

There are no recommended Phase 4 commitments for these two NDAs from the chemists.

The chemistry review for NDA 21-471 is not finished as of the time of this Division Director Memo.

Pharmacology/Toxicology:

See the review by Dr. Jiaqin Yao. No new studies were reviewed with this submission. Pharmacology/toxicology data for [redacted] when the sunscreen was being developed for [redacted] all non-clinical studies within these curren[redacted] ubmissions were previously included in [redacted]; there were 87 animal and toxicology studies under the [redacted] evelopment program. (See page 9 of Dr. b(4)

Shetty's review.) The pharmacology/toxicology review for these ——pplications is duplicated or adapted from —— b(4)

Ecamsule absorbs light at wavelengths from approximately 290 to 400 nm with a maximum absorption at 344 nm. The review of the data shows that the new active ingredient, ecamsule, has low acute and repeat dose toxicity. Essentially no toxicity was observed in rats after chronic oral dosing with ecamsule or after chronic topical dosing with the ecamsule in minipigs. Ecamsule appears to be negative for genotoxic potential and was negative in a 2-year dermal carcinogenicity assay in mice. UV induction of skin tumor formation in hairless mice was not increased by ecamsule, the sunscreens containing three active ingredients, ——Cream. — b(4)
The conclusions of the Carcinogenicity Assessment Committee that met August 30, 2005 to consider were that an adequate carcinogenicity study was performed and that there were no drug-related tumor findings.

Based upon the preclinical data, ecamsule is not a teratogen. In a fertility study in rabbits treated with ecamsule, a slight but statistically significant decrease in the percentage of implantation sites with live concepti and a slight but statistically significant increase in post- implantation loss were observed in females but no evidence of adverse effects on reproductive and developmental parameters in rats and rabbits was noted. No sensitization was detected in guinea pigs tested with ecamsule in aqueous solution.

Dr. Yao concluded that the NDA is approvable from a pharmacology/toxicology perspective and that no additional non-clinical studies are needed.

Microbiology:
See the review by Dr. Stephen E. Langille. The drug products are all non-sterile topical creams containing methylparaben and propylparaben preservatives and no deficiencies were noted by the reviewer. He recommended approval from the standpoint of product microbiology quality and did not recommend the need for any Phase 4 studies.

Clinical Pharmacology/Biopharmaceutics: b(4)
See the following two reviews by Dr. Abimbola Adebowale:

- o ——
- o NDAs 21-501, 21-502, and 21-471 dated February 21, 2006

The applicant provided the previously submitted in vivo data for —— b(4)
—— cream and the previously submitted in vitro permeation data to evaluate the impact of reformulation (triad products against the tetrad product) on the bioavailability of ecamsule. The agency found this approach acceptable (documented in the minutes for the end of Phase 2 meeting held on January 24, 2001).

The pharmacokinetic data based upon single and multiple topical applications of —— to the trunk, arms and legs demonstrated minimal systemic b(4)
exposure. For 152 of 154 samples obtained in the study of six male healthy volunteers, the plasma concentration of ecamsule was below the limit of quantitation (1 ng/ml). Two

(21 CFR 352 subpart D). The studies to assess water resistance are also appropriate and acceptable in that they were performed in accordance with the testing procedures outlined in 21 CFR 352 subpart D that necessitate that SPF values should be accurate following 40 minutes of water immersion (21 CFR 352.76).

FDA has not published a final rule specifying testing procedures for evaluating the UVA radiation protection of sunscreens. However, FDA has published comments regarding UVA protection. As stated in the 1993 TFM, a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

- The absorption spectrum extends to 360 nm or above in the UVA range
- UVA protection is demonstrated using an appropriate testing procedure

There have been additional TFM amendments published on UVA testing. In a 1998 TFM amendment, FDA found a method based on determination of a minimal response dose (MRD) which uses pigment darkening rather than erythema (as used in SPF testing) to be an acceptable testing method (63 FR 56584 at 56587). Dr. Koenig comments that two of the sponsor's UVA clinical studies were conducted using the persistent pigment darkening method (PPD) which is nearly identical to the MRD method. As stated in that 1998 TFM, until FDA proposes a UVA protection test method, FDA "considers testing procedures similar to the UVA protection factor method...and those methods described by R.W. Gange et al. and N. J. Lowe et al. as adequate for determining the UVA protection potential of a finished OTC sunscreen drug product" (63 FR 56584 at 56587). Dr. Koenig states that the sponsor's third clinical UVA study was conducted using the 8-methoxypsoralen (8-MOP) method, which is comparable to the FDA-accepted methods of Lowe, et al. and Gange, et al. In studies using synthetic human skin, the sponsor demonstrated that all three formulations effectively absorb UV light at wavelengths ≥ 360 nm.

The monograph allows for labeling of sunscreens for adults and children at least 6 months of age but does not specify the ages of study participants that need to enroll in the efficacy studies. The monograph states that male and female subjects need to be enrolled, but does not state that they must be enrolled in equal numbers, just that they must have fair skin with skin types I, II, and III (21 CFR 352.72). The populations enrolled in the efficacy studies had a preponderance of females and an age range of 18 years to 65 years. Dr. Koenig notes that there is no apparent anatomical or physiological difference between male and female skin, or the skin of adults and children (at least 6 months old) to suggest that there may be a difference in the efficacy of a sunscreen for these groups.

Dr. Koenig concludes that the effectiveness of the three sunscreen formulations containing ecamsule in combination with the other generally recognized as safe and effective sunscreen active ingredients is acceptable for OTC marketing. The formulations provide effective protection against UVB and UVA radiation. The formulations in NDAs 21-501 and 21-471 are effective after 40 minutes of water immersion.

The Division of Dermatologic and Dental Products (DDDP) was requested to provide oversight on the clinical efficacy review of the [redacted] sunscreen products. The DDDP concluded that Dr. Koenig's recommendation that these products should be approved for OTC use for the prevention of [redacted] induced by UVB and UVA radiation should be implemented. b(4)

Dermal Safety Studies:
See the review by Dr. Phyllis A. Huene.
The sponsor conducted an irritation and contact sensitization study, a photosensitization study, and a phototoxicity study using the three [redacted] unscreen formulations.
Dr. Huene concludes that the dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. She comments that although there were no sensitization reactions at challenge, one subject in the sensitization study was apparently pre-sensitized to the test products prior to study initiation. Thus, there is some potential for sensitization and the product labeling should address this.

For the acnegenicity/comedogenicity study (PEN.570.01), the sponsor used only the formulation which is the subject of NDA 21-502 (active ingredients: ecamsule 2%, avobenzone 2%, and octocrylene 10%). The sponsor concludes that the results indicate that this formulation is non-acnegenic and non-comedogenic. Dr. Huene disagrees, noting that although the mean values for acne lesions and comedones decreased from baseline, there were increased lesions of both types in one or more subjects, as indicated by the range of values. She suggests that there may be a subset of subjects in which the test product might be acnegenic/comedogenic.

The sponsor also conducted a comedogenicity study to assess the comedogenicity potential of two of the formulations (NDA 21-501 and NDA 21-471) by determining the densities of microcomedones on follicular biopsies after repeated patch applications. Microcomedones are microscopically visible precursors of comedones and their presence is determined by stereomicroscopic examination of follicular biopsies. The evaluation of comedogenicity was based on a comparison of the mean microcomedone score between the test material and the untreated control. The sponsor concluded that, under the conditions of the study, both formulations were non-comedogenic. Dr. Huene concluded that the study is interesting from a theoretical standpoint, but has no regulatory utility, as it did not utilize clinical parameters. Dr. Huene states that the acnegenicity/comedonegenicity studies are not adequate to conclude that the test products are not acnegenic or comedogenic [redacted] b(4)

Safety:
See the review by Dr. Daiva Shetty.
The sponsor submitted safety data from a total of 28 clinical studies. The sponsor organized the studies into three groups:

- Phase 1, 2, 3
- Long term

- Supportive

The sponsor states that variations among the three formulations addressed in this review [redacted] are minor, and, as such, much of the safety information is common to all. Since the safety data provided to support the marketing of all three [redacted] formulations is the same, Dr. Shetty reviewed the data for the different NDAs en mass. b(4)

A total of 2539 study subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phases of these sunscreens. There were no drug-related deaths or drug-related serious adverse events (AE) reported among the participants in the clinical trials. A total of 31 subjects in the clinical studies discontinued due to AEs. Twelve of them discontinued because of AEs that may have been drug related. All of these possibly, probably, or definitely drug related AEs were local skin irritations and all resolved.

Eighty-six of the 1155 subjects in the Phase 1, 2, and 3 clinical studies experienced 125 AEs. Of these, seven (skin infection, pruritis, eczema) were assessed as probably or possibly related to treatment and they were all mild and non-serious. A total of 1048 subjects had long-term exposure (12-month studies) to one of the ecamsule-containing sunscreen formulations. The average combined long term exposure for the long term studies for the three formulations that are the subject of this review plus the [redacted] was 213 days (range 1 – 393 days). b(4)

For the three [redacted] formulations, 66 drug-related AEs were reported (skin and appendages system) and 4 additional drug-related AEs occurred in the Special Senses System. None were assessed as serious and all resolved. The profile of drug-related AE was consistent across the 3 long-term [redacted] tudies, except for PEN.750.01 (ecamsule 2%; avobenzone 2%; octocrylene 10%) in which a higher number of acne events were reported. Dr. Shetty states that this may have been related, in part, to the higher number of adolescents enrolled in this study. (Also relevant may be Dr. Huene's observation, in her dermal safety review, that there may be a subset of the population in which the product is acnegenic.) The most common treatment-related AEs in these three long-term [redacted] studies were: acne, dermatitis, dry skin, eczema, erythema, pruritus, skin discomfort and sunburn. Among 336 subjects in the supportive [redacted] studies, were seven reports of probably related erythema/edema and four possibly related reports of papules. b(4)

Dr. Shetty notes that the sunscreen products were inadvertently applied to abnormal skin in some study participants. These participants had a higher incidence of cutaneous adverse events. Dr. Shetty states that the proposed label appropriately directs consumers to stop use of the product if a rash or irritation develops and lasts, but she recommends that the labeling should also carry a warning to use caution when applying the sunscreen on damaged skin.

Dr. Shetty comments that the [redacted] 12-month safety study RD.06.SRE.18047 was reviewed in detail under [redacted] by Dr. Huene on January 29, 2004. Except for b(4)

sunburn, adverse events which were considered to be possibly related to the study products were of low incidence and minor severity. Four vascular birthmarks in infants born to pregnant women who participated in this study were noted. (See the Pregnancy section below). b(4)

Dr. Shetty's review reflects that post marketing AEs reported to the sponsor did not reveal serious safety issues and the most common AEs in the post marketing database were consistent with the AE profile from the clinical trials. Dr. Shetty's review of the medical literature did not reveal new safety concerns.

Pediatrics:

The efficacy studies did not enroll subjects under the age of 18 years. Dr. Koenig notes that, ideally, the studies would have enrolled pediatric subjects, however, it is not unreasonable to extrapolate the findings to children 6 months or older as labeled under the sunscreen monograph. There is no apparent anatomical or physiological difference between the skin of adults and children 6 months or older that suggests there may be significant differences in protection provided by a sunscreen.

FDA requested that the sponsor enroll 100 children, ages 6 months to 12 years of age in the long term safety study assessing the SFP 15 water resistant product (NDA 21-501). In fact, 179 children 6 months to 12 years enrolled of whom 57 were 2 years of age or younger. An additional 24 children between 12 and 17 years also participated in this study. FDA also requested that the sponsor enroll 100 children ages 6 months to 12 years of age in the long term safety study assessing the SPF 20 water resistant product (NDA 21-471); the sponsor enrolled 64 children under twelve of whom 24 were 2 years of age or younger. The long term safety study assessing the SPF 15 non-water resistant product (NDA 21-502) enrolled 78 children ages 12 – 17. The overall pediatric population for the integrated safety summary included 243 children ages 6 months to 12 years and an additional 115 adolescents. No specific association between adverse reactions and pediatric use was noted by Dr. Shetty.

The Division of Nonprescription Clinical Evaluation consulted the Division of Pediatric Drug Development for their advice concerning the need for pediatric studies in infants less than 6 months of age for the two sunscreen products (NDAs 21-501 and 21-502). (See the consultation from Dr. Lisa Mathis.) Because the American Academy of Pediatrics and the Australian Cancer Society acknowledge that sunscreen may need to be occasionally applied to small areas of infant skin such as the face and back of hands, and there is no evidence that sunscreens are safe in the age group < 6 months, Dr. Mathis recommends that the safety of the new sunscreen products be demonstrated in infants < 6 months of age. Also, given that clinical pharmacology studies have not been conducted with — products in infants and that there is greatest potential for systemic absorption in young infants given their high body surface area to body weight ratio, she recommends that pharmacokinetic data be obtained in infants < 6 months of age. She comments that it is important that these products be studied in infants with

healthy skin. She also recommends that [redacted] b(4)

[redacted] I concur with Dr. Mathis' recommendations to study infants, however it would not be surprising if the sponsor has trouble enrolling young infants for the requested pharmacokinetic studies because of the multiple blood sampling needed.

Pregnancy:

The monograph labeling for sunscreens does not include a pregnancy warning (21 CFR 352.52). The proposed labeling for the three [redacted] NDAs does not carry a pregnancy warning. Ecamsule is Pregnancy Category B, based upon pre-clinical data. b(4)

Eleven study participant women became pregnant. Four infants of mothers using [redacted] developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot. Because of hemangiomas in two infants that were born to mothers using the [redacted] product while pregnant, in her review, Dr. Shetty recommends a Phase IV controlled study in pregnant women to evaluate the relationship between sunscreen exposure during pregnancy and vascular skin abnormalities in babies. She makes this recommendation despite the negative animal teratogenicity and reproductive function studies, the lack of human systemic absorption of ecamsule under maximized conditions of exposure, and the high background incidence of vascular skin abnormalities in babies. b(4)

Drs. Phyllis Huene and Jonathan Wilkin in their reviews of the [redacted] comment on the vascular lesions seen in infants born to women in the long term safety study. Dr. Wilkin notes that vascular formations are fairly common in neonates and that estrogen has been theorized to play a role. He states that although some sunscreens have been weakly positive in bioassays of estrogenicity, ecamsule has not been evaluated beyond standard reproductive toxicology studies, avobenzone is considered inactive in estrogenicity tests, and no data are available for the other two filters regarding estrogenicity. In her review, Dr. Huene recommends that there should be a post-marketing commitment to evaluate children of mothers exposed to the product during pregnancy for cutaneous vascular abnormalities. Dr. Wilkin's division director memo recommends that the applicant should evaluate post-marketing data in other jurisdictions to see whether there is a signal for congenital vascular neoplasms/malformations associated with the use of component UV filters or chemically-related UV filters as part of the [redacted] In his division director memorandum, Dr. Wilkin did not consider the congenital vascular lesions in infants to be an approvability issue. b(4)

Post-marketing data in other jurisdictions was submitted as part of the safety data supplied to the NDAs for the three [redacted] sunscreen formulations and Dr. Shetty did not pick up any safety signals regarding vascular lesions in neonates. It is important to note that the ecamsule-containing products are marketed as a cosmetic in most foreign jurisdictions, and as a drug in Canada and Australia. It is unclear how effective the post-marketing reporting systems, especially in those markets where the sunscreens are

cosmetics, would be in capturing an association between sunscreen use and vascular skin lesions. Dr. Shetty's review of the medical literature did not reveal safety signals for vascular lesions.

The Division of Nonprescription Clinical Evaluation consulted the Division of Pediatric Drug Development and the Pregnancy and Lactation Team (PLT) to provide feedback on whether or not the sponsor should conduct studies to evaluate children of mothers exposed to the new sunscreen formulations during pregnancy for cutaneous vascular abnormalities and for advice b(4) See the consultation from Drs. Susan McCune and Diane Kennedy.

Upon a review of study data, the FDA adverse events reporting system data, and the medical literature, the Division of Pediatric Drug Development and the PLT concluded, in their January 31, 2006 review, that cutaneous vascular abnormalities occur frequently in newborns. The literature suggests that hemangiomas are seen in approximately 7-10% of the newborn population. The PLT consultation states that unless the two cases of hemangiomas reported in the one study (RD.06.SRE.18047) which was reviewed for the b(4) are unusual for some reason, e.g., very large, life threatening, deep, etc., the PLT does not see a need for a pregnancy exposure registry.

One of the two babies had two small hemangiomas; one was raised and the other was flat. These were considered to be of mild severity. The second baby had a strawberry hemangioma the investigator considered to be of moderate severity. The lesion was located in the perianal area and the baby received pulse-dye laser treatment which slowed the lesion's growth. The child was said to be developing well.

Dr. Lawrence Eichenfield, M.D., Chief, Pediatric and Adolescent Dermatology, Children's Hospital and Health Center and the University of California, San Diego School of Medicine also reviewed the neonate vascular lesion cases. He stated that hemangiomas occur in 10% to 13% of children in the first year of life, and to the best knowledge of experts, have not been reported to be induced by exogenous factors such as drugs or chemicals. He concluded that the vascular birthmarks reported in the b(4) trials were probably random findings not related to the use of the cream during pregnancy. After internal discussion with Dr. Shetty, a pediatrician, as well as the medical reviewer who looked at the safety data, neither of these lesions appears to meet the unusual criteria defined by the PLT that would trigger the need for a pregnancy exposure registry.

The PLT concluded that the nevus flammeus case was considered of unlikely relationship to the study treatment and note that this lesion is present in approximately half of all newborns. Café au lait spots are seen in approximately 10% of all newborns.

b(4)

- Negative reproductive toxicology findings in animals
- < 1% systemic absorption of ecamsule
- No evidence of reproductive toxicity for titanium oxide, ecamsule, avobenzone, or octocrylene in the literature
- No literature reports or AERS reports of hemangiomas associated with the use of titanium oxide, ecamsule, avobenzone, or octocrylene.

Considering the totality of the available data, I support this recommendation and do not see the need for a pregnancy registry or other types of Phase 4 studies targeted to assess pregnancy-related adverse events.

Labeling:

See the labeling review by Dr. Michael Koenig for NDAs 21-501 and 21-502. The sponsor submitted labeling for the two sunscreens to be marketed under a total of twelve trade names. The two sunscreens have identical trade names in four cases, and thus eight novel trade names have been proposed for the two NDAs. He recommends that the eight trade names proposed for these products are acceptable.

The Division sent the sponsor many labeling comments based upon the clinical recommendations of the reviewers, the recommendations of the Division of Medication Errors and Technical Support, and also the need to comply with the formatting requirements of the Drug Facts label for NDAs 21-501 and 21-502. These comments are detailed in Dr. Koenig's review and I concur with them.

In Dr. Abimbola Adebowale's review, she commented that based on the documented interactions in the literature between sunscreens and estradiol topical emulsion and DEET, the following label is recommended: "Ask your doctor or pharmacist before use if you are using a topical prescription estrogen product, such as Estrasorb or a non-prescription insect repellant."

The Division of Nonprescription Regulation Development is working on a proposed rule to address combination sunscreen-insect repellant products, but there are still issues to resolve. Regarding topical prescription estrogen products, Estrasorb is the only one Dr. Koenig could find that mentions absorption problems with concurrent use of sunscreens. He recommends that all sunscreens should not be labeled based on an interaction with one estradiol product, and that instead, the Estrasorb product should carry a sunscreen warning. I agree with this view.

CONCLUSION:

The data supports that these three — sunscreen formulations are safe and effective when used as directed. There are no unsettled issues related to pharmacology/toxicology, microbiology, or clinical pharmacology/biopharmaceutics. The products are effective. However, the NDA 21-502 — SPF 15 Sunscreen is not water resistant. This product should include the labeling to reapply as needed after towel drying, swimming, or perspiring (which the sponsor has added to the water resistant formulation labeling) so consumers achieve desired efficacy over the course of the day.

b(4)

The products may be more irritating if applied to damaged skin and so the labeling should include a warning not to use on broken skin or serious burns. Further, application of the product to skin where the barrier has been compromised may impact the pharmacokinetics of the creams. The data does not support non-comedogenic labeling.

Based upon the clinical pharmacology and biopharmaceutical data, the pharmacology/toxicology data, the lack of signal in the post-marketing data, the lack of signal in the published literature, and the recommendations by the PLT, it does not appear that the sunscreen NDAs need a pregnancy warning, phase IV studies to assess vascular lesions in babies of pregnant women, or a pregnancy exposure registry.

The sponsor should study the pharmacokinetic and safety of these products in infants < 6 months of age because infants in this age category could benefit from availability of a nonprescription sunscreen. Currently nonprescription sunscreens are labeled down to the age of 6 months. Thus the sponsor should not be granted a waiver for this age category.

The chemistry analyses and labeling were performed for the two NDAs, 21-501 and 21-502. The chemistry analysis supports that these are creams, not lotions and the labeling should reflect this. The —— inspection is not yet complete and must be acceptable for the two NDAs to be approved. The sponsor has many labeling deficiencies to correct before this product can be approved. b(4)

A DSI inspection was requested for NDA 21-471, but not for NDA 21-501 and NDA 21-502. This inspection is pending as of the date of this Division Director Memorandum.

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/s/

Andrea Segal
3/6/2006 12:16:04 PM
MEDICAL OFFICER

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: Consult received: February 27, 2006
Consult completed: March 3, 2006

FROM: Jean Temeck, M.D.
Acting Medical Team Leader
Division of Pediatric Drug Development

THROUGH: Lisa Mathis, M.D.
Acting Division Director
Division of Pediatric Drug Development

TO: Andrea Leonard-Segal, M.D.
Acting Division Director
Division of Nonprescription Clinical Evaluation

SUBJECT: Determination of the need for pediatric studies in infants less than 6 months of age for two sunscreen products, ' — SPF 15 water resistant (W/R) lotion (NDA 21-501) and — SPF 15 lotion (NDA 21-502). Include the rationale for your decision. The Sponsor is requesting approval to market both sunscreen products in the OTC setting for daily use in children 6 months of age and older and in adults. b(4)

Background and Review

L'Oreal submitted NDA 21-501 for — SPF 15 W/R lotion on May 16, 2005 and for NDA 21-502 for — SPF 15 lotion on May 12, 2005. The PDUFA goal dates are March 16, 2006 and March 12, 2006, respectively. b(4)

The active ingredients in these products include 2% avobenzone and 10% octocrylene which are among the sunscreen active ingredients that are generally recognized as safe and effective (GRASE) as listed in the OTC sunscreen drug monograph (21 CFR part 352). The third active ingredient is ecamsule at a concentration of 3% in — SPF 15 W/R lotion and 2% in — SPF 15 lotion. Ecamsule is a new molecular entity in the United States although it has been marketed in Europe and other parts of the world since 1993. b(4)

These products were recommended for approval from the Chemistry, (pending an acceptable recommendation from the Office of Compliance for inspection of the — ———— , Clinical Pharmacology, Pharmacology/Toxicology and Clinical efficacy and safety perspectives. b(4)

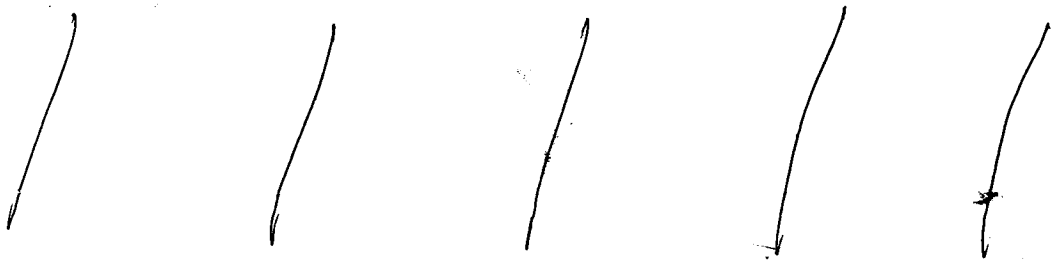
It should be noted that clinical pharmacology studies were not conducted with the [redacted] products. The Sponsor provided clinical pharmacology data for a related product, [redacted] the three active ingredients contained in [redacted] SPF 15 W/R lotion. These data demonstrated minimal systemic exposure in the human after single and repeated topical administration of [redacted] cream. Specifically, data were submitted from a maximum exposure study, 1.CG.03.SRE.2607, conducted in healthy adult male volunteers after single and multiple applications of about 15g of [redacted] cream per application (approximately 1 mg/cm^2). The plasma levels of ecamsule were below the quantification limit (1 ng/ml) in all but 2 of 154 samples. The maximum concentration of ecamsule obtained was 1.95 ng/ml. The Sponsor also submitted data from two supportive studies also conducted in healthy adult male volunteers using different formulations of ecamsule. These studies also demonstrated minimal systemic absorption of ecamsule. The first was a pharmacokinetic (PK) study, V99.1203, using 2% radio-labeled ecamsule. The systemic absorption after a single topical application, estimated from the radioactivity levels in the urine, feces and skin was less than 0.1% of the applied dose. In the second PK study, V3156, conducted with a non radio-labeled 4.95% ecamsule formulation, for a five-day repeated topical application, unchanged ecamsule was not detected in the urine. b(4)

The Clinical Pharmacology reviewer stated that based on the maximum systemic exposure of ecamsule in man (~2 ng/ml) and the estimated maximal exposure level demonstrated in two animal species treated orally with ecamsule without showing toxic effects (~1,000 ng/ml), the safety margin for the systemic exposure of ecamsule in the adult is ~500-fold. The review further stated that given the higher body surface are to weight in children, the safety margin in adults should be divided by a factor of 1.3-1.4 to estimate the safety margin in children (Nohynel et al, 2001). Based on this factor, the safety margin in children would be >350-fold. However, the Pharmacology/Toxicology reviewer stated that adequate data were not available to determine the safety margin in humans. Nevertheless, as elucidated below, the safety of ecamsule and [redacted] cream from the preclinical perspective was demonstrated. b(4)

The Pharmacology/Toxicology reviewer concluded that the nonclinical studies showed that the new active ingredient, ecamsule, and [redacted] cream had low acute and repeat dose toxicity. Essentially no toxicity was observed after chronic topical dosing of ecamsule solutions (up to 24%) or [redacted] cream in minipigs or after chronic oral dosing with ecamsule in rats. The reviewer noted that the NOAEL for oral ecamsule in rats after 26 weeks was at least 1,000 mg/kg/day. Ecamsule appeared to be negative for genotoxic potential and it was negative, at concentrations up to 26%, in a 2-year dermal carcinogenicity study in mice. The reproductive toxicology studies demonstrated a slight but statistically significant decrease in the percentage of implantation sites with live concepti and a slight but statistically significant increase in post-implantation loss in female rats at the 1,000 mg/kg dose but no effect was seen at the 100 and 300 mg/kg doses. There was no other evidence of adverse effects on reproductive and developmental parameters in rats and rabbits. b(4)

The [redacted] product clinical program to demonstrate efficacy enrolled adult subjects while the safety program also included pediatric subjects at the request of FDA. The Medical Officer's review of the safety profile of [redacted] SPF 15 W/R lotion (NDA 21-501) and [redacted] SPF 15 lotion (NDA 21-502) demonstrated that these sunscreen products are safe for OTC use in children, 6 months of age and older, and in adults. Information was primarily extracted from the Clinical Safety Review of NDAs 21-501 and 21-502 by Dr. D. Shetty, dated 1/6/06. When information was extracted from the MO review by Dr. P. Huene for [redacted]

b(4)



Overview of the Clinical Safety Program:
19 Phase 1, 2 and 3 clinical studies that enrolled 1,155 adult subjects (i.e. >18 years of age). 1,094 subjects completed these studies;
4 Phase 3 long-term safety studies that enrolled a total of 1,048 adult and pediatric subjects and with 730 completers and
5 supportive studies that enrolled 336 adult subjects of whom 317 were completers.

Total number of death in all studies: in the entire clinical safety program, there was only 1 death- an intentional injury in a 13 year old female that was unrelated to study treatment.

Any serious adverse event, except death, reported in any clinical study: according to the MO safety reviewer, Dr. D. Shetty, a total of 32 subjects experienced serious adverse events. All occurred in the long-term safety studies. The review does not specify the nature of these adverse events but states that all of them were unrelated to study treatment.

(Note: per the MO review of study RD.06.SRE.18047 which was submitted under [redacted], 18 subjects experienced serious adverse events. One was dermatological and 17 were non-dermatological. The specific nature of these adverse events was not specified).

b(4)

Treatment-emergent adverse events:
In the Phase 1, 2 and 3 clinical studies, 7 (0.6%) adverse events (skin infection, pruritus and eczema) were assessed as possibly or probably related to treatment. All were non-serious and of mild severity.

In the three [redacted] long-term studies (750.01, 750.02 and 750.03), which enrolled a total of 573 patients, there were 60 treatment-related adverse events reported in the Skin and Appendages System. These included 16 (2.8%) dermatitis; 12 (2.1%) acne; 6 (1.0%) sunburn; 5 (0.9%) each of eczema, erythema, pruritus and skin discomfort; 3 (0.5%) dry

b(4)

skin; 2 (0.3%) seborrhea and 1 (0.2%) rosacea. There were 4 treatment-emergent adverse events in the Special Senses System: 3 (0.5%) conjunctivitis and 1 (0.2%) taste perversion. None of these adverse events were assessed by the investigator as serious and all of them resolved.

The review of the long-term safety study, RD.06.SRE.18047, submitted with — — did not specifically address treatment-emergent adverse events other than to state that the reviewer did not consider any of the serious adverse events to be related to —

b(4)

In the — supportive studies, there were 7 (2.1%) events of erythema/edema that were considered to be probably related and 4 (1.2%) of papules that were considered to be possibly related to study treatment.

Specific Information Provided for the Long-term Studies which Included Pediatric Patients:

A total of 358 pediatric subjects, aged 6 months to 18 years of age, were included in the four long-term safety studies. The study numbers, total sample size (N), formulation used and the number of subjects enrolled by age subsets are depicted in the table below:

b(4)

	PEN.750.01 N= 248	PEN.750.02 N= 246	PEN.750.03 N= 79	RD.06.SRE. 18047 N= 475
Formulation	— SPF 15	— SPF 15 WR	— SPF 20 WR[a]	— cream[b]
# (%) patients enrolled by age:				
0.5 to ≤2 yrs.	0 (0%)	57 (23.2%)	24 (30.4%)	0 (0%)
>2 to ≤6 years	0 (0%)	60 (24.4%)	32 (40.5%)	0 (0%)
>6 to ≤12 years	0 (0%)	62 (25.2%)	8 (10.1%)	0 (0%)
12 to ≤18 years	78 (31.5%)	24 (9.8%)	2 (2.5%)	11 (2.3%)
>18 yrs. (adult)	170 (68.5%)	43 (17.5%)	13 (6.5%)	464 (97.7%)

b(4)

The treatment duration in these 3 long-term safety studies combined were, by age, as follows:

Age Group	Mean ± S.D. (days)	Median (range) days
0.5 to ≤2 years	57.79 ± 68.92	31.0 (1-312)
2 to ≤ 6 years	67.45 ± 80.32	36.0 (1-363)
6 to ≤12 years	87.59 ± 99.05	37.5 (1-350)
12 to ≤18 years	247.67 ±145.40	344.0 (1-371)
18 to ≤65years	250.24 ±142.51	346.0 (1-376)
>65 years	308.31 ±117.58	360.5 (2-372)

Comment: The above table demonstrates that treatment duration was shorter for children (aged ≤12 years) than for adolescents and adults and that duration of exposure of adolescents to sunscreen was comparable to adults.

The MO safety reviewer stated that a total of 19 subjects discontinued the long-term studies due to adverse events. 6 of these 19 were pediatric subjects. The adverse events were death in one subject (intentional injury in a 13 year old female, unrelated to study treatment), rash in 3 subjects (assessed as definitely related), one photosensitivity (possibly related) and one urticaria (unlikely related).

The MO safety reviewer compared the incidence of treatment related adverse events by age subsets in the 3 — long-term safety studies as follows: b(4)

	Drug Related Adverse Events	
	Dermatological	Non-Dermatological
Age subgroup:		
0.5 to ≤2 years (n= 81)	3 (3.7%)	1 (1.2%)
>2 to ≤6 years (n= 92)	8 (8.7%)	0 (0%)
>6 to ≤12 years (n= 70)	5 (7.1%)	0 (0%)
>12 to ≤18 years (n= 104)	7 (6.7%)	0 (0%)
>18 years (n= 226)	31 (18.8%)	7 (6.8%)

Comment on the above table:
The incidence of drug-related adverse events, both dermatological and non-dermatological, were lower in pediatric subjects (0.5 to 18 years) compared to adults. Specifically, the incidence of drug related dermatological adverse events was 6.6% in pediatric subjects compared to 13.7% in adults. The corresponding incidences for drug related non-dermatological adverse events were 0.3% and 3.1%. Dr. Shetty mentioned that these differences in incidence may be related to differences in duration of use.

Predisposing conditions:
The MO safety review also mentioned that the — products should be applied only to healthy skin. The reviewer provides data (Table 24, pp. 43) that demonstrated a higher incidence of adverse events, the majority of which were dermatological, when these products were applied to the skin of subjects with predisposing conditions such as atopic/dry skin. An example is provided of a 14 month old boy with a history of eczema who experienced worsening eczema on the back of the neck upon application of — SPF 20 WR to this site. The event resolved with topical hydrocortisone. When the b(4)

sunscreen was subsequently applied to other areas of the body, no sequelae were observed.

Post-marketing adverse events:
Per Dr. Shetty's review, there were no new safety signals.

The annual incidence of adverse events spontaneously reported to the L'Oreal Cosmetovigilance System for all ecamsule-containing products over the period 1993-2003 was relatively stable over time, ranging from 0.011% in 1993 to 0.002% in 1995, with an incidence rate of 0.0045% in 2003. The nature of the adverse events was similar to those reported in the clinical studies (see Dr. Shetty's review, Table 13, pp. 29). Six serious adverse events were retrospectively identified. Four of these were reported in children and included erythema and edema of the skin; edema of the face and eyes with rash; breathing difficulty and swelling of the face and eyes in a child with a history of asthma; and sore throat (strep)/swollen eyes and rash. The remaining 2 cases were an anaphylactic reaction (swollen eyes and tightness of the chest and throat) in an adult and urticaria in a subject of unspecified age.

b(4)

The Sponsor also submitted pediatric adverse events spontaneously reported to the L'Oreal Cosmetovigilance System with use of sunscreens containing any of the ingredients found in the — products (octocrylene, Mexoryl SX, avobenzone and titanium dioxide). A total of 386 adverse events were reported in children, aged 1 to 16 years, between 1996 (when the products were first marketed) and 2004. There was a gradual increase in the number of adverse event reports, from 1 in 1996 to 102 in 2004. The Sponsor associated this increasing trend with increased use of sunscreen products. The majority of reactions occurred within several hours after the first application and the majority resolved within 3 days. No permanent sequelae were reported. All the reactions were limited to the sunscreen application site. The most common adverse events (in decreasing order of frequency) were erythema, papules, edema, dryness, "eczema" and urticaria-like lesions. In some cases, these symptoms were accompanied by pruritus or a "burning sensation".

A search of the AERS database conducted by Dr. S. McCune (see her review dated 1/31/06 in response to a consult requested from The Pregnancy and Lactation Team) for ecamsule, avobenzone, octocrylene, titanium dioxide and — revealed a total of 61 reports. There were no AERS mentions for any children between 0-1 years of age.

b(4)

Literature Review:
The MO safety reviewer summarizes several articles submitted by the Sponsor highlighting the occurrence of photoallergic reactions to the active ingredients in sunscreens. Dr. Shetty mentions that photoallergic reactions to sunscreens are a well known adverse effect.

Literature review by DPDD:

The American Academy of Pediatrics (AAP)[1] states that the safety of sunscreen use in infants less than 6 months of age is controversial. Concerns cited include the possibility of different absorptive characteristics of skin in infants younger than 6 months and immaturity of biological systems that metabolize and excrete drugs. However, the AAP points out that the Australian Cancer Society, supported by the Australian College of Dermatologists, has concluded that that there is no evidence to suggest that using sunscreen on small areas of a baby's skin is associated with any long-term effects. They recommend their use when physical protection, e.g. clothing, hats and shade, is not adequate[2]. The AAP states that on reflective surfaces, an umbrella or canopy may reduce UVR exposure by only 50%. The AAP urges that parents be informed of the importance of avoiding high-risk sun exposure. They further state that it may be reasonable to apply sunscreen to small areas of the infant's skin that is not adequately protected by clothing, such as the face and backs of the hands.

The updated version of the Australian Cancer Society's Position Statement on this issue[3] again reiterates that there is no evidence that using sunscreen in infants is harmful[4]. They recommend that infants, 0-12 months of age, be kept out of the sun as much as possible. They state: "If infants are kept out of the sun or are well protected from UV radiation by clothing, hats and shade, then sunscreen need only be used occasionally on very small areas of an infant's skin." The Australian Cancer Society's recommendations are specifically as follows:

-minimize the infant's exposure to the sun, particularly between 10 am and 3 pm;
-cover the infant's skin as much as possible with loose-fitting clothes and tightly woven wraps;
-choose a hat that will protect the baby's face, neck and ears;
-make use of available full shade and use material that will cast a dark shadow to shade the infant's pram, stroller or play area;
-regular check the infant's clothing, hat and shade positioning to ensure that the infant continues to be well protected from UV radiation;
-apply a SPF 30+ broad spectrum water resistant sunscreen to small areas of skin that cannot be protected by clothing (e.g. face, ears, backs of hands). Apply sunscreen 20 minutes before going outside and reapply every couple of hours or more often if it has been wiped or washed off.

Potential side effects of sunscreen use in infants that are mentioned in this position statement include minor skin irritation and allergic contact dermatitis from preservatives or perfumes in the product. They mention that sunscreen milks or creams formulated for sensitive skin usually contain titanium dioxide or zinc oxide and are less likely to contain alcohol or fragrances that may irritate the skin. They recommend that use be stopped immediately in the event of occurrence of an unusual reaction.

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[1] American Academy of Pediatrics Committee on Environmental Health. Ultraviolet Light: A Hazard to Children. Pediatrics 1999;104(2):328-333.

[2] Australian Cancer Society. *Policy Statement: Babies and Sunscreen.* Sydney, Australia: Australian Cancer Society; 1998.

[3] Cancer Council Australia and The Australian College of Dermatologists. *Position Statement. Sun Protection and Infants (0-12 months).* May 2005.

[4] Marks R. The Use of Sunscreens in the Prevention of Skin Cancer. Cancer Forum 1996;20:211-215.

Marks (see reference 4) mentions that when sunscreen is applied to small areas of infant skin, it is unlikely that there will be enough absorption of sunscreen to constitute an excess load for hepatic metabolism.

Robinson JK et al[5] emphasize the importance of not directly exposing infants to the sun before 6 months of age. Morelli JG and Weston WL[6] make the point that there is no compelling reason for infants less than 6 months of age to have sun exposure prolonged enough to require sunscreens. They further mention that sunscreen use in infants may give parents a false sense of security and make it more likely that the infant will be exposed to the sun for longer periods of time than without sunscreen. It is, therefore, imperative that the guidelines as outlined by the AAP and the Australian Cancer Society are followed if sunscreen is applied to young infants.

De Simone[7] mentions that there is "little data" available to help healthcare providers make informed decisions regarding the best sunscreen products to use in infants less than 6 months of age although the Sunscreen OTC monograph recommends that a physician be consulted regarding use of sunscreen in this age group.

Conclusions and Recommendations (note: recommendations are bolded below)
Both the AAP and The Australian Cancer Society acknowledge that sunscreen may need to be *occasionally applied* to *small areas of infant skin* such as the face or backs of the hands. They do emphasize the importance of non-chemical protective measures and avoiding/minimizing exposure of young infants to the sun as the primary protective measures. While there is no evidence that sunscreens are harmful to infants under 6 months of age, there is no direct evidence that they are safe in this age group. The safety of the ~ sunscreen products has been adequately demonstrated from both a preclinical and clinical perspectives in subjects 6 months of age and older. **The safety of these products needs to be demonstrated in those infants younger than 6 months of age.** As pointed-out by Dr. D. Shetty, **it is important that these products be studied in infants with healthy skin** because skin conditions such as eczema which is prevalent in young infants may be exacerbated by application of sunscreen to affected areas. Although absorption of these products appears to be minimal, detectable blood levels of a comparable sunscreen drug product, ~ was detected in 2 adult subjects. Also, given that clinical pharmacology studies have not been conducted with ~ products in any age group and that there is greatest potential for systemic absorption in young infants given their high body surface area to body weight ratio, **it is recommended that pharmacokinetic data also be obtained in this age group.** The data obtained from the pharmacokinetic and safety studies will be critical to practitioners

b(4)

[5] Robinson JK et al. Meeting Report. Executive summary of the national "Sun Safety: Protecting Our Future" Conference: American Academy of Dermatology and Centers for Disease Control and Prevention. New York, New York, May 1 and 2, 1997. Journal of the American Academy of Dermatology 1998;38 (no. 5, part 1):774-780.
[6] Morelli JG and Weston WL. What Sunscreen Should I Use for My 3-Month-Old Baby? Pediatrics 1993;9(6):882.
[7] DeSimone EM. FDA Proposes Changes in Sunscreen Regulations. American Pharmacy 1994; volume NS34, No.6:26-31.

who are consulted by parents and caregivers regarding use of sunscreen products in infants less than 6 months of age. **Furthermore, consideration should be given to providing additional precautions in OTC labeling of sunscreen products if they are approved for use in infants less than 6 months of age so that parents and caregivers understand the appropriate place of these products in protecting young infants from UV radiation.**

b(4)

OVERSIGHT OF CLINICAL EFFICACY REVIEW

Application Type	NDAS
Submission Number	21-501, 21-502, 21-471
Submission Code	N-000
Letter Date	May 16, 2005: NDA 21-501 May 12, 2005: NDA 21-502 September 27, 2005: NDA 21-471
Stamp Date	May 16, 2005: NDA 21-501 May 12, 2005: NDA 21-502 September 28, 2005: NDA 21-471
PDUFA Goal Date	March 16, 2006: NDA 21-501 March 12, 2006: NDA 21-502 July 28, 2006: NDA 21-471
Reviewer Name	Phyllis A. Huene, M.D.
Review Completion Date	January 30, 2006
Established Names	Ecamsule, Avobenzone, Octocrylene, Titanium dioxide
(Proposed) Trade Name	Several
Therapeutic Class	Sunscreen agents
Applicant	L'Oreal USA Products, Inc
Priority Designation	S
Formulation	b(4)
Dosing Regimen	Application 15 minutes before sun exposure
Indication	Sun protection
Intended Population	age 6 months and older

Oversight of Clinical Efficacy review b(4)
Phyllis A. Huene, M.D.
NDAs 21-501, 21-502, 21-471
[redacted] Sunscreens

The Division of Dermatologic and Dental Products has been requested to provide oversight on the clinical efficacy review of the [redacted] b(4) sunscreen products (NDAs 21-501, 21-502, 21-471), done by Michael Koenig, Ph.D.

On review of Dr. Koenig's evaluation of the test data on protection from UVB and UVA radiation, it is apparent that the standards for approval differ for prescription and for OTC sunscreen products in such particulars as the demonstration of the contribution of each ingredient, description of the methodology, the number of subjects tested, independent confirmation of the results, and more.

However, Dr. Koenig's review appears to be in conformance with the OTC regulations and review policies for sunscreen products, and so his recommendations that these products should be approved for OTC use for the prevention of [redacted] b(4) should be implemented.

Phyllis A. Huene, M.D.

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/s/

Phyllis Huene
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MEDICAL OFFICER
Efficacy Review Addendum on SPF and UVA protection - Dermatology Evaluation

Stanka Kukich
2/15/2006 05:59:28 PM
MEDICAL OFFICER

CLINICAL EFFICACY REVIEW

Application Type	NDA
Submission Number	21,501, 21-502, and 21-471 (IND 59,126)
Submission Code	N000
Letter Date	May 16, 2005 (NDA 21-501) May 12, 2005 (NDA 21-502) September 27, 2005 (NDA 21-471)
Stamp Date	May 16, 2005 (NDA 21-501) May 12, 2005 (NDA 21-502) September 28, 2005 (NDA 21-471)
PDUFA Goal Date	March 16, 2006 (NDA 21-501) March 12, 2006 (NDA 21-502) July 28, 2006 (NDA 21-471)
Reviewer Name	Michael L. Koenig, Ph.D.
Review Completion Date	December 27, 2005
Established Name	**NDA 21-501**: Ecamsule, 3%; avobenzone, 2%; octocrylene, 10% **NDA 21-502**: Ecamsule, 2%; avobenzone, 2%; octocrylene, 10% **NDA 21-471**: Ecamsule, 2%; avobenzone, 2%; octocrylene, 10%, titanium dioxide, 2%
(Proposed) Trade Name	Several
Therapeutic Class	Sunscreen
Applicant	L'Oreal USA Products Inc.
Priority Designation	S
Formulation	Lotions
Dosing Regimen	**NDAs 21-501 and 21-471**: Apply 15 minutes before sun exposure & reapply as needed or after towel drying, swimming, or perspiring

	NDA 21-502: Apply evenly to cleansed skin before sun exposure and as needed
Indication	Prevention of sunburn [redacted] due to sun exposure by providing broad spectrum protection from UVB and UVA radiation b(4)
Intended Population	Adults and children 6 months of age and older

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Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on effectiveness, the following products should be approved for over-the-counter (OTC) use for prevention of [redacted] nduced by UVB and UVA radiation: b(4)

- SPF 15 water resistant sunscreen lotion (NDA21-501)
- SPF 15 sunscreen lotion (NDA 21-502)
- SPF 20 water resistant sunscreen lotion (NDA 21-471)

Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers in the Office of Nonprescription Products and Division of Dermatologic and Dental Drug Products.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This review only considers the effectiveness of the three formulations in NDAs 21-501, 21-502, and 21-471. Therefore, this section is not applicable.

1.2.2 Required Phase 4 Commitments

There are no phase 4 requirements with respect to efficacy.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

L'Oreal is seeking approval to market three OTC sunscreen drug products for daily use by adults and children six months of age and older:

- SPF 15 water resistant sunscreen lotion (NDA 21-501)
- SPF 15 sunscreen lotion (NDA 21-502)
- SPF 20 water resistant sunscreen lotion (NDA 21-471)

Two of the products (NDAs 21-501 and 21-502) include 2% avobenzone, 10% octocrylene, and the new molecular entity ecamsule at different concentrations. The other product (NDA 21-471)

includes these three active ingredients plus — titanium dioxide. Each sunscreen product contains the new molecular entity, ecamsule. Although it has been marketed outside the United States since 1993, ecamsule is a new molecular entity in the United States. The other active ingredients (octocrylene, avobenzone, and titanium dioxide) are among the 16 generally recognized as safe and effective (GRASE) sunscreen active ingredients listed in the OTC sunscreen drug monograph (21 CFR part 352). b(4)

In support of its submission, the sponsor has submitted data from a total of three pre-clinical and 12 clinical studies. Since the pre-clinical and clinical data to support the marketing of the three products are the same, the three NDAs are being evaluated concurrently for efficacy in this review.

1.3.2 Efficacy

Based on my review of the twelve clinical and three in vitro studies submitted in these NDAs, this reviewer concludes that all three formulations provide effective protection from —— due to both UVB and UVA radiation. The three formulations meet the criteria for UVB radiation protection in 21 CFR 352.20(a) in that:

- the concentration of each active ingredient contributes a minimum SPF of not less than 2 to the finished products
- each finished product has an SPF value that exceeds the number of sunscreen active ingredients in the product multiplied by 2

Because the formulations meet these criteria, they may be labeled as providing effective UVB protection. Furthermore, the sunscreens in NDAs 21-501 and 21-471 may bear water resistance claims, because the testing procedures in 21 CFR 352.76(a) were followed for these formulations.

The three formulations also meet the criteria outlined in the 1993 tentative final monograph (TFM) for OTC sunscreen drug products making claims of UVA protection. In that rulemaking, FDA stated that a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

- the absorption spectrum extends to 360 nm or above in the UVA range
- UVA protection is demonstrated using an appropriate testing procedure

The products to be marketed under NDAs 21-501, 21-502, and 21-471 may bear UVA protection claims, such as "broad spectrum" or "protects against UVA rays or radiation" (58 FR 28194 at 28233), but they may make no claims as to the degree of UVA protection. The sponsor proposes the use of a UVA rating termed the "PFA" (protection factor for UVA), which is analogous to the SPF for UVB protection, but FDA does not recognize this as a valid measure of the extent of UVA protection. FDA is currently drafting a proposed rule regarding UVA testing and labeling. When FDA finalizes a UVA protection rating under the OTC sunscreen monograph, the formulations may be labeled according to the monograph.

2.1 Product Information

NDA 21-501 was submitted for the SPF 15 water resistant (WR) sunscreen lotion. This product is a topical sunscreen composed of the following three active ingredients:

- Avobenzone, 2%
- Octocrylene, 10%
- Ecamsule (Mexoryl®), 3%

The sponsor requests that this formulation be marketed under five different brand names:

1. UV EXPERT
2. SOLAR EXPERTISE
3. ANTHELIOS
4. b(4)
5. CAPITAL SOLEIL

These products will be marketed in tubes. Throughout this review, SPF 15 WR sunscreen lotion is referred to as formulation 760-006.

NDA 21-502 was submitted for the SPF 15 sunscreen lotion. This product is a topical sunscreen composed of the same three active ingredients in formulation 760-006:

- Avobenzone, 2%
- Octocrylene, 10%
- Ecamsule (Mexoryl®), 2%

The only difference between this product and formulation 760-006 is the concentration of ecamsule (and inactive ingredient). The sponsor requests that this formulation be marketed under seven brand names:

1. UV PROTECTIVE FACIAL MOISTURIZER
2. UV ACTIV
3. ANTHELIOS
4. HYDRAPHASE UV
5. UV EXPERT
6. SOLAR EXPERTISE
7. UV DEFENDER

The first three products/brand names will be marketed in tubes. The last four products/brand names will be marketed in pump bottles. Throughout this review, SPF 15 sunscreen lotion is referred to as formulation 539-009.

NDA 21-471 was submitted for the SPF 20 WR sunscreen lotion. This product is a topical sunscreen composed of the following four active ingredients:

- Avobenzone, 2%
- Octocrylene, 10%
- Ecamsule (Mexoryl®), 2%
- Titanium dioxide, 2%

The only difference between this product and formulation 539-009 is the addition of titanium dioxide (and inactive ingredient concentrations). The sponsor requests that this formulation be marketed under four brand names:

1. CAPITAL SOLEIL
2. ANTHELIOS
3. UV EXPERT
4. SOLAR EXPERTISE

Throughout this review, SPF 20 WR sunscreen lotion is referred to as formulation 539-106.

The sponsor is proposing to market the three sunscreen products in the OTC setting for daily use by adults and children six months of age and older. The sponsor states that the products will be marketed in accordance with OTC sunscreen drug monograph (21 CFR part 352).

2.2 Currently Available Treatment for Indications

There are a total of 16 sunscreen active ingredients generally recognized as safe and effective (GRASE) under the OTC sunscreen drug monograph (21 CFR part 352). All sunscreens currently available for OTC use in the United States are marketed under the sunscreen monograph. Three of the active ingredients included in these sunscreen formulations (avobenzone, octocrylene, and titanium dioxide) are listed as GRASE in the sunscreen monograph both as single active ingredients and in combination with other sunscreen active ingredients.

2.3 Availability of Proposed Active Ingredient in the United States

As mentioned in section 2.2, three of the active ingredients contained in the sunscreen formulations are currently available in the United States OTC market. The only ingredient not currently available in the United States is ecamsule.

2.4 Important Issues With Pharmacologically Related Products

There are no known serious safety or efficacy issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

The three formulations were developed under IND 59,126. In addition to IND 59,126, the sponsor studied ecamsule under [redacted] b(4)

b(4)

The sponsor sought regulatory guidance and advice from FDA on several occasions during the development of these three formulations. All issues raised by FDA during pre-NDA meetings have been adequately addressed by the sponsor.

2.6 Other Relevant Background Information

In 1991, ecamsule was included in the European Economic Community (EEC) Cosmetic Directory, Annex VII, "List of UV Filters Which Cosmetic Products May Contain." Subsequently, marketing of sunscreen products containing ecamsule began in Europe and other parts of the world in 1993. According to the sponsor, over ——— units of sunscreen products containing ecamsule have been sold worldwide during that time. b(4)

Sunscreen products, also known as UV filters, are regulated as cosmetics in all other countries except Canada and Australia. Ecamsule was registered with the Canadian Health Protection Bureau in 1994 and with the Australian Heath Authorities in 1995.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review is pending.

3.2 Animal Pharmacology/Toxicology

The sponsor conducted a total of 87 animal and toxicology studies as part of the ——— development program ——— These studies did not demonstrate that ecamsule was teratogenic, carcinogenic, or photocarcinogenic. There was no embryolethality or reproductive toxicity associated with ecamsule alone or in combination with other sunscreen active ingredients. The acute oral toxicity dose is 5000 mg/kg in the rat and 2000 mg/kg in the mouse. b(4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data to support the effectiveness of the three formulations was submitted in NDAs 21-501 (volumes 74-80), 21-502 (volumes 74-80), and 21-471 (volumes 75-81). Data include 12 single center, controlled, randomized, double-blinded studies. Eight of the studies were conducted under the supervision of Dr. Robert W. Shanahan at the Consumer Product Testing

Company, Inc. (CPTC) in Fairfield, NJ. Four of the studies were conducted under the supervision of Dr. Alan H. Greenspan at TKL Research, Inc. (TKL) in Paramus, NJ.

In response to a request from FDA (End of Phase 2 Meeting Minutes, April 16, 2001), the sponsor also submitted three in vitro (i.e., non-clinical) studies designed to demonstrate that the absorption spectra of the three formulations extend to wavelengths ≥ 360 nm (i.e., long-wavelength UVA). One of the studies was conducted under the supervision of Dr. Robert W. Shanahan at CPTC in Fairfield, NJ. The other two studies were conducted at L'Oreal Applied Research and Development Laboratories in Clichy and Chevilly-Larue, France.

As additional evidence that the three formulations are effective UVB and UVA sunscreens, the sponsor references seven clinical studies submitted on May 29, 2003, to support the effectiveness b(4) Cream contains the same active ingredients contained in the three formulations currently under review.

Data supporting the safety of the three formulations is included in the 12 clinical effectiveness studies. Safety data is also derived from nine clinical studies designed specifically to evaluate the safety of the three formulations that are the subject of this review and four safety studies conducted to support the safety of b(4)

4.2 Tables of Clinical Studies (Efficacy Only)

Table 1. UVB Protection

Study	Formulation 760-006 (NDA 21-501)	Formulation 539-009 (NDA 21-502)	Formulation 539-106 (NDA 21-471)	Study Center
PEN.810.01		✓		TKL
PEN.810.02		✓		CPTC
PEN.810.03			✓	TKL
PEN.810.04			✓	CPTC
PEN.810.05	✓	✓	✓	CPTC
PEN.810.06	✓	✓	✓	CPTC

Table 2. Water Resistant UVB Protection

Study	Formulation 760-006 (NDA 21-501)	Formulation 539-009 (NDA 21-502)	Formulation 539-106 (NDA 21-471)	Study Center
PEN.820.01	✓		✓	TKL
PEN.820.02	✓		✓	CPTC
PEN.99001.01.COS	✓			CPTC

Table 3. UVA Protection

Study	Formulation 760-006 (NDA 21-501)	Formulation 539-009 (NDA 21-502)	Formulation 539-106 (NDA 21-471)	Study Center
PEN.910.01	✓	✓	✓	CPTC
PEN.910.02	✓	✓	✓	CPTC
PEN.920.01	✓	✓	✓	TKL

Table 4. In Vitro UVA Absorption Studies

Study	Formulation 760-006 (NDA 21-501)	Formulation 539-009 (NDA 21-502)	Formulation 539-106 (NDA 21-471)	Study Center
S01-0205	✓	✓	✓	CPTC
D20041030	✓	✓	✓	L'Oreal
SOL-DP1-97-021	✓		✓	L'Oreal

4.3 Review Strategy

Safety data is being reviewed separately by Daiva Shetty, M.D., in the Office of Nonprescription Products and Phyllis Huene, M.D., in the Division of Dermatological and Dental Drug Products.

This review evaluates the 12 clinical efficacy studies submitted under NDAs 21-501, 21-502, and 21-471. FDA reviewed the efficacy data submitted for [redacted] on January 29, 2004. Therefore, these data are not being reviewed at this time. The review will first evaluate the nine clinical studies submitted to demonstrate that the three formulations provide protection against UVB radiation. The review discusses six studies examining static (i.e., not water resistant) UVB protection (PEN.810.01 through PEN.810.06) in section 6.1, followed by three studies conducted to determine the water resistant SPF of formulations 760-006 and 539-106 in section 6.2. After evaluating UVB protection, the review discusses three clinical studies submitted to demonstrate UVA radiation protection (PEN.910.01, PEN.910.02, and PEN.920.01) in section 6.3. Finally, three in vitro studies submitted to demonstrate that the three formulations absorb UVA light at wavelengths $\geq$ 360 nm are discussed in section 6.4.

4.4 Data Quality and Integrity

A request was submitted to the Division of Scientific Investigations (DSI) to inspect CPTC in Fairfield, NJ. This study center was selected for inspection because eight of the 12 clinical studies and one of the three in vitro studies were conducted by CPTC. The results of the inspection are pending.

4.5 Compliance with Good Clinical Practices

Institutional Review Boards (IRBs), as defined in 21 CFR part 56, approved the protocols and informed consent forms (ICFs) for all clinical studies. No changes in the conduct of the studies were allowed without prior written approval from the sponsor and approval by the IRB.

The sponsor indicates that study investigators obtained written consent from all subjects in accordance with 21 CFR 50.20, 50.25, and 50.27. The sponsor further states that the study investigator or a delegated staff member explained the nature of the study, including any associated risks, to each subject before the subject signed the ICF. The explanations of the study occurred privately with adequate time to answer any questions from study subjects.

The sponsor states that all of the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practice and were in compliance with local, state, and federal regulatory requirements.

4.6 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators of all but three clinical studies had no financial interests in these products, the studies, or the companies conducting the studies. The three studies for which certifications were not provided were previously reviewed under [redacted]. None of the studies are pivotal for the evaluation of either efficacy or safety for the three sunscreen formulations submitted under NDAs 21-501, 21-502, and 21-471. b(4)

5 CLINICAL PHARMACOLOGY

Clinical pharmacology studies are not pertinent to this review of efficacy. These studies are being evaluated by other reviewers.

5.1 Pharmacokinetics

Pharmacokinetics studies are not pertinent to this review of efficacy. Three in vivo and four in vitro pharmacokinetics studies are being evaluated by other reviewers.

5.2 Pharmacodynamics

No pharmacodynamic data were submitted in the three NDAs.

5.3 Exposure-Response Relationships

The three NDAs did not include studies exploring exposure-response relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor states that the three products are indicated "for prevention of sunburn —— —— following chronic exposure to ultraviolet radiation." This indication includes both a UVB and UVA radiation protection claim. The UVB claim is essentially "helps prevent sunburn/protects against UVB radiation." This UVB claim is allowed for OTC sunscreens marketed under the OTC drug monograph system (21 CFR 352.52(b)(1)). b(4)

6.1.1 Methods

An assessment of the effectiveness of a sunscreen formulation in protecting against UVB radiation is based on the criteria outlined in the OTC sunscreen final monograph published on May 21, 1999 (*Federal Register*, vol. 64, pp. 27666-27693). In accordance with 21 CFR 352.10 and 352.20, OTC sunscreen drug products must have a minimum SPF value of not less than the total number of sunscreen active ingredients in the formulation multiplied by two. For example, an OTC sunscreen drug product containing four active ingredients must have an SPF of at least 8 (i.e., 4 multiplied by 2). In addition, each active ingredient must contribute an SPF of at least 2 to the SPF of the finished product.

The method for determining the SPF value (*i.e.*, effectiveness) of an OTC sunscreen drug product marketed in the United States is detailed in 21 CFR part 352 subpart D. As indicated in § 352.72, at least 20 evaluable subjects must complete the study. Sunscreen formulations are applied to $\geq$50 cm^2 test sites on each subject's back. Each test site is further subdivided into at least 3 subsites no less than 1 cm^2 in size. Each subsite is exposed to a different amount of simulated solar radiation. Sunscreen formulations are applied to the entire test site using a finger cot to ensure an even distribution of 2 mg/cm^2. Subjects are not exposed to UV radiation for at least 15 minutes after applying sunscreen formulations.

A standard sunscreen with a known SPF value is tested concurrently with each test formulation to ensure the test results are valid. A standard formulation containing 8 percent homosalate is prepared as described in § 352.70. The SPF of this standard formulation should be 4.47 ± 1.28 and the 95 percent confidence interval for the mean SPF of the standard formulation should include the value 4.

Solar radiation is simulated with a light source emitting UV radiation over the range of 290 to 400 nm (i.e., UVB and UVA radiation). The solar simulator must be calibrated periodically to ensure that subjects are exposed to the spectrum of UV radiation defined in § 352.71.

Subjects are exposed to a geometric series of increasing amounts of radiation (§ 352.73(b)) in the absence or presence of a sunscreen to determine the MED_{US} (MED unprotected skin) or MED_{PS} (MED protected skin), respectively. MED is defined as the amount of light energy required to

produce the "first perceptible, redness reaction with clearly defined borders 22 to 24 hours after exposure" (§ 352.73(c)). Therefore, MED_{US} is always lower than MED_{PS}, because less UV radiation is required to produce redness (i.e., erythema) in the absence of a sunscreen than in the presence of a sunscreen.

SPF is defined as the ratio of MED_{PS} to MED_{US} (§ 352.73(c)). Thus, sunscreen effectiveness directly correlates to the SPF value. SPF values are determined for each of the subjects enrolled in the study, and a mean SPF value is calculated for the group. Variability about the mean is estimated by calculating the standard deviation and the 95% confidence interval. The labeled SPF value of a test formulation is the largest whole number less than the lower limit of the 95% confidence interval.

6.1.2 General Discussion of Endpoints

The endpoint in these studies is erythema (redness) induced by simulated solar radiation. By determining the amount of radiation necessary to produce erythema on each subject's back in the presence and absence of a sunscreen, an SPF value can be calculated for the sunscreen. The SPF was first allowed by FDA over thirty years ago (*Federal Register*, vol. 43, pp. 38206-38269). SPF is recognized by FDA and other regulatory bodies around the world as a valid and appropriate measure of sunscreen effectiveness against UVB radiation. Furthermore, U.S. consumers recognize SPF as the measure of protection against sunburn, which is caused primarily by UVB radiation.

6.1.3 Study Design

These studies were designed to strictly adhere to the SPF testing procedures outlined in the OTC sunscreen drug monograph (21 CFR part 352 subpart D). According to the monograph, study subjects must meet all of the following criteria:

- be fair-skinned (i.e., skin type I, II, or III)
- in good health
- not taking medicines that might produce abnormal sunlight response
- have no "sunburn, suntan, scars, active dermal lesions, [or] uneven skin tones" on the parts of the back to be tested

Skin types are defined in 21 CFR 352.72(a)(1):

- Type I: always burns easily; never tans
- Type II: always burns easily; tans minimally
- Type III: burns moderately; tans gradually (light brown)
- Type IV: burns minimally; always tans well (moderate brown)
- Type V: rarely burns; tans profusely (dark brown)
- Type VI: never burns; deeply pigmented

Thus, the study design appropriately excludes U.S consumers that do not frequently sunburn. The testing procedure in the monograph suggests that studies should include males and females, but does not specify the numbers of males and females required or any other demographic criteria.

The submitted studies include more female than male subjects, with some studies enrolling only females. The ages of subjects evaluated in these studies range from 18 to 65. Ideally, the studies would enroll equal numbers of males and females as well as pediatric subjects. However, it does not seem unreasonable to extrapolate the findings to males or to children over 6 months (as labeled under the sunscreen monograph). There is no apparent anatomical or physiological difference between female and male skin or the skin of adults and children (over 6 months) that suggest there may be significant differences in protection provided by a sunscreen for these groups.

Because FDA developed the OTC sunscreen drug monograph, the studies are adequate and well-controlled as defined in 21 CFR 314.126. Therefore, the study design provides a reasonable assessment of benefit.

6.1.4 Efficacy Findings

6.1.4.1 Study PEN.810.01

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on April 26, 2000, and concluded on June 9, 2000. A total of 21 evaluable subjects completed the study. All of the subjects were female with an age range of 22 to 58 years (average age of 42 years). The subjects had skin type I, II, or III.

This study evaluates the effectiveness of formulation 539-009 (NDA 21-502) which consists of the following active ingredients:

- 2% ecamsule
- 10% octocrylene
- 2% avobenzone

In accordance with the 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly.

The principal investigator reports no deviations from the IRB-approved protocol.

The mean SPF of the standard sunscreen was reported to be 4.44 with a standard deviation (SD) of 0.69. This falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF $\pm$ SD of test formulation 539-009 was 16.65 ± 3.57. The 95% confidence interval ranged from 15.3 to 17.9, resulting in a labeled SPF of 15 (21 CFR 352.73(d)).

Test formulation 539-009 appears to be an effective sunscreen against UVB radiation on adult females. It is expected that the formulation is also effective on males and children (over two years). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an

SPF value greater than 2 times the number of active ingredients (i.e., 15 > 2 times 3). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies PEN.810.05 and PEN.810.06.

6.1.4.2 Study PEN.810.02

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on July 31, 2000, and concluded on August 16, 2000. A total of 20 evaluable subjects completed the study. Fifteen subjects were female and five were male. The subjects ranged in age from 19 to 55 years (average age 33.3 years) and had skin type I, II, or III.

As in study PEN.810.01, this study evaluates the effectiveness of formulation 539-009 and includes the concomitant testing of an 8% homosalate standard sunscreen.

The principal investigator reports only one deviation from the IRB-approved protocol. Subject 03- — had their MED evaluated approximately 25 hours after exposure to irradiation. The investigator notes that this evaluation should have occurred between 22 and 24 hours after irradiation (21 CFR 352.72(h)). This reviewer does not consider this minor deviation to have affected the study results. b(6)

The mean SPF ± SD of the standard sunscreen was reported to be 4.44 ± 0.45. This falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of test formulation 539-009 was 17.45 ± 2.78. The 95% confidence interval ranged from 16.15 to 18.75, resulting in a labeled SPF of 16 (21 CFR 352.73(d)).

Test formulation 539-009 appears to be an effective sunscreen against UVB radiation in both males and females. It is expected that the formulation is also effective on children (over 6 months of age). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e., 16 > 2 times 3). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies PEN.810.05 and PEN.810.06.

6.1.4.3 Study PEN/810.03

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on August 6, 2000, and concluded on September 20, 2000. A total of 20 evaluable subjects completed the study. All of the subjects were female with an age range of 19 to 63 years (average age 43.4 years) and had skin type I, II, or III.

This study evaluates the effectiveness of formulation 539-106 (NDA 21-471) which consists of the following active ingredients:

- 2% ecamsule
- 10% octocrylene
- 2% avobenzone
- 2% titanium dioxide

In accordance with the 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly.

The principal investigator reports one deviation from the IRB-approved protocol. Subject — /06 participated in a consumer study 24 days prior to the start of the study. This reviewer considers the deviation to be minor and agrees with the investigator that it did not affect the study results. b(6)

The mean SPF ± SD of the standard sunscreen was reported to be 4.03 ± 0.69. This falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of test formulation 539-106 was 24.90 ± 4.01. The 95% confidence interval ranged from 23.35 to 26.45, resulting in a labeled SPF of 23 (21 CFR 352.73(d)).

Test formulation 539-009 appears to be an effective sunscreen against UVB radiation in females. It is expected that the formulation is also effective on males and children (over 6 months of age). The formulation meets the criterion specified in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e., 23 > 2 times 4). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies PEN.810.05 and PEN.810.06.

6.1.4.4 Study PEN.810.04

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on August 24, 2000, and concluded on September 23, 2000. A total of 21 evaluable subjects completed the study. Sixteen subjects were female and five were male. The subjects ranged in age from 20 to 61 years (average age 39.7 years) and had skin type I, II, or III.

As in study PEN.810.03, this study evaluates the effectiveness of formulation 539-106 and includes the concomitant testing of an 8% homosalate standard sunscreen.

The principal investigator reports no deviations from the IRB-approved protocol.

The mean SPF ± SD of the standard sunscreen was reported to be 4.77 ± 0.86. This falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of test formulation 539-106 was 31.70 ± 3.80. The 95% confidence interval ranged from 29.97 to 33.44, resulting in a labeled SPF of 29 (21 CFR 352.73(d)).

Test formulation 539-106 appears to be an effective sunscreen against UVB radiation in both males and females. It is expected that the formulation is also effective on children (over 6 months of age). The formulation meets the criterion in 21 CFR 352.20(a) that it have an SPF value greater than 2 times the number of active ingredients (i.e., 29 > 2 times 4). The contribution of each active ingredient to the effectiveness of the finished product, as required by 21 CFR 352.20(a), is addressed in studies PEN.810.05 and PEN.810.06.

6.1.4.5 PEN.810.05

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on April 2, 2002, and concluded on April 24, 2002. A total of 49 evaluable subjects completed the study. Thirty-three subjects were female and sixteen were male. The subjects ranged in age from 18 to 65 years (average age 36.1 years). They had skin type I, II, or III. Each subject was randomly assigned three test products and the standard sunscreen, such that each of six test products was tested on at least 20 subjects.

This study was designed to evaluate the effectiveness of six test formulations containing various combinations of the active ingredients in formulations 760-006, 539-009, and 539-106. All test formulations consisted of the same vehicle, with the only difference being the active ingredients and, in some instances, b(4)

The following table outlines the composition of each test formulation and the number of subjects tested with each formulation. Three of the test formulations represent final formulations submitted under NDAs 21-501, 21-502, and 21-471.

b(4)

Table 5. Composition of Test Formulations in Study — 810.05

b(4)

Test Formulation	10% Octocrylene		2% Avobenzone	2% Ecamsule	3% Ecamsule	2% Titanium dioxide	Number of subjects
A	✓						25
B	✓		✓				25
C	✓		✓	✓			24
D (539-009)	✓		✓	✓			24
E (760-006)	✓		✓		✓		24
F (539-106)	✓		✓	✓		✓	25

In accordance with 21 CFR Section 352.70, an 8% homosalate standard sunscreen was tested concomitantly.

The principal investigator reports four deviations from the IRB-approved protocol:

- The MED for one subject was scored 24.5 hours post-irradiation.
- The MED for one subject was scored 21 hours and 52 minutes post-irradiation.
- The MED for one subject was scored at 25 hours and 20 minutes post-irradiation.
- One subject ingested two tablets of Tylenol Cold and Flu medicine during the study.

This reviewer agrees with the principal investigator that these deviations do not interfere with the study results.

The mean SPF ± SD for each test formulation and concurrently run standard sunscreen are presented in the table below. The table also includes the labeled SPF value for each test formulation. In accordance with 21 CFR 352.73(d), the labeled SPF equals the largest whole number less than the lower limit of the 95% confidence interval.

Table 6. SPF Values for Formulations Tested in PEN.810.05

Test Formulation	Mean SPF ±SD	Labeled SPF	Standard Sunscreen Mean SPF ± SD
A	8.50 ± 1.13	8	4.47 ± 0.85
B	12.47 ± 1.33	12	4.68 ± 0.89
C	17.55 ±2.57	16	4.69 ± 0.77
D (539-009)	18.55 ±2.64	17	4.7 ± 0.95
E (760-006)	18.93 ± 2.72	17	4.64 ± 0.87
F (539-106)	23.02 ± 2.62	22	4.47 ± 0.79

The mean SPF ± SD of the standard sunscreen ranged from 4.47 ± 0.85 to 4.70 ± 0.95. These values fall within the acceptable range specified in 21 CFR 352.70(a). Therefore, the study results are valid.

This study evaluated the effectiveness of individual active ingredients contained in formulations 760-006, 539-009, and 539-106. According to 21 CFR 352.20(a), the SPF of the final formulation must be equal to or greater than two times the number of active ingredients. Formulations 760-006 (test formulation E) and 539-009 (test formulation D) contain three active ingredients, requiring an SPF of at least 6. Formulations 760-006 and 539-009 both produced SPF values of 17. Formulation 539-106 (test formulation F) contains four active ingredients and, therefore, requires an SPF of at least 8. The labeled SPF for this formulation was determined to be 22. Thus, all three formulations meet one of the two effectiveness criteria specified in 21 CFR 352.20(a).

In addition, 21 CFR 352.20(a) requires that each active ingredient contribute a minimum SPF of not less than 2 to the finished product. In this study, formulation 539-009 (test formulation D) produced an SPF of 17. Comparing this formulation to test formulation B indicates that 2% ecamsule contributes an SPF of 5 to formulation 539-009. By comparing test formulation A to test formulation B, it appears that 2% avobenzone contributes an SPF of 4. Finally, test formulation A produced an SPF of 8, indicating that 10% octocrylene contributes an SPF of 8 to formulation 539-009. Thus, formulation 539-009 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective. It is also interesting to note that, as evidenced by comparing test formulation D to test formulation C, ____ is not an active ingredient (i.e., _____did not contribute SPF of at least 2). b(4)

Formulation 760-006 also met both effectiveness criteria in this study. Formulation 760-006 (test formulation E) produced an SPF of 17. Comparing this formulation to test formulation B indicates that 3% ecamsule contributes an SPF of 5 to formulation 760-006. By comparing

test formulation A to test formulation B, it appears that 2% avobenzone also contributes an SPF of 4. Finally, test formulation A produced an SPF of 8, indicating that 10% octocrylene contributes an SPF of 8 to formulation 760-006. Thus, formulation 760-006 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective.

Finally, formulation 539-106 met both effectiveness criteria. Comparing formulation 539-106 (test formulation F) with test formulation C shows that 2% titanium dioxide contributes an SPF of 6. The contributions of the three other active ingredients in this formulation have already been described in the discussion of formulation 539-109.

6.1.4.6 Study PEN.810.06

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on June 26, 2002, and concluded on August 15, 2002. A total of 97 evaluable subjects completed the study. Of the original 100 subjects enrolled in the study, 66 subjects were female and 34 were male. One subject (#90/ —) requested to be withdrawn from the study, and two subjects (#5/ — and #53/ —) were excluded because they were taking exclusionary concomitant medications. The subjects ranged in age from 18 to 63 years (average age 36.9 years) and had skin type I, II, or III. Each subject was randomly assigned two test products and two standard sunscreens, such that each of the seven test products was tested on at least 20 subjects. b(6)

This study was designed to evaluate the effectiveness of seven test products containing various combinations of the individual active ingredients in formulations 760-006, 539-009, and 539-106. All test formulations consisted of the same vehicle, with the only difference being the active ingredients and the ——— b(4)

Table 7. Composition of Test Formulations in Study —.810.06

b(4)

Test Formulation	10% Octocrylene		2% Avobenzone	2% Ecamsule	3% Ecamsule	2% Titanium dixoide	Number of subjects
607-76A	✓		✓			✓	23
607-12A	✓		✓				24
607-20A	✓		✓	✓			25
607-27A (539-009)	✓		✓	✓			25
607-34A (760-006)	✓		✓		✓		23
607-41A (539-106)	✓		✓	✓		✓	25
607-67A	✓		✓				23

In accordance with the 21 CFR 352.70, a standard sunscreen was tested concomitantly. In this study, the standard sunscreen consisted of an 8% homosalate preparation (SPF 4). The study also included an SPF 15 standard sunscreen to ensure that determinations of SPF greater than 15 were valid.

The principal investigator reports 34 deviations from the IRB-approved protocol. Twenty-six subjects had different evaluators assess MED_{US} and MED_{PS}. Six subjects had readings outside the 22-24 hour post-irradiation window (five had readings ranging from 7 to 40 minutes early; one had a reading 25 hours post-irradiation). One subject was exposed to slightly lower doses of UV radiation than others in the test group, but an SPF could still be accurately determined. One subject was incorrectly irradiated at one subsite. This reviewer concurs with the principal investigator's assertion that none of these deviations would have significantly affected the study results.

The mean SPF ±SD for each test formulation and concurrently run standard sunscreen are presented in the table below. The table also includes the labeled SPF value for each test formulation. In accordance with 21 CFR 352.73(d), the labeled SPF equals the largest whole number less than the lower limit of the 95% confidence interval.

Table 8. SPF Values for Different Formulations Tested in — .810.06 b(4)

Test Formulation	Mean SPF ± SD	Labeled SPF	SPF 4 Sunscreen Mean SPF ± SD	SPF 15 Sunscreen Mean SPF ± SD
607-76A	17.24 ± 1.89	16	4.33 ± 0.48	15.07 ± 1.57
607-12A	11.16 ± 1.69	10	4.38 ± 0.60	15.52 ± 1.75
607-20A	17.10 ± 2.84	16	4.37 ± 0.57	15.13 ± 1.30
607-27A (539-009)	16.14 ± 2.16	15	4.40 ± 0.65	15.03 ± 1.59
607-34A (760-006)	18.11 ± 1.42	17	4.44 ± 0.55	15.04 ± 1.40
607-41A (539-106)	24.88 ± 3.03	23	4.58 ± 0.49	15.40 ± 1.70
607-67A	10.99 ± 1.04	10	4.41 ± 0.49	15.97 ± 1.59

The mean SPF ± SD of the SPF 4 standard sunscreen ranged from 4.38 ± 0.60 to 4.58 ± 0.49. These values fall within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of the SPF 15 standard sunscreen ranged from 15.03 ± 1.59 to 15.97 ± 1.59. These standard sunscreens indicate that the study results are valid.

Like — 810.05, this study evaluated the effectiveness of individual active ingredients contained in formulations 760-006, 539-009, and 539-106. According to 21 CFR 352.20(a), the SPF of the final formulation must be equal to or greater than two times the number of active ingredients. Formulations 760-006 (test formulation 607-34A) and 539-009 (test formulation 607-20A) contain three active ingredients, requiring an SPF of at least 6. Formulations 760-006 and 539-009 produced SPF values of 17 and 16, respectively. Formulation 539-106 contains four active ingredients and, thus, should have an SPF of at least 8. The labeled SPF for this formulation was 23. Therefore, all three formulations meet one of the two effectiveness criteria specified in 21 CFR 352.20(a).

In addition, 21 CFR 352.20(a) requires that each active ingredient contribute a minimum SPF of not less than 2 to the finished product. In this study, formulation 539-009 (test formulation 607-27A) produced an SPF of 15. Comparing this formulation to test formulation 607-67A indicates that 2% ecamsule contributes an SPF of 5 to formulation 539-009. The individual contributions of 10% octocrylene and 2% avobenzone cannot be determined in this study, but from the results for study PEN.810.05, it seems that these ingredients contribute SPFs greater than 2 in the same vehicle. Thus, formulation 539-009 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective. It is also interesting to note that, as evidenced by comparing formulation 539-009 to test formulation 607-20A, —— is not an active ingredient (i.e., ———— did not contribute an SPF of at least 2). b(4)

Formulation 760-006 also met both effectiveness criteria in this study. Formulation 760-006 (test formulation 607-34A) produced an SPF of 17. Comparing this formulation to test formulation 607-12A indicates that 3% ecamsule contributes an SPF of 7 to formulation 760-006. Again, as noted above, the individual contributions of 10% octocrylene and 2% avobenzone cannot be determined in this study, but from the results for study PEN.810.05, these ingredients seem to contribute SPFs greater than 2 in the same vehicle . Thus, formulation 760-006 meets both criteria in 21 CFR 352.20(a) and, therefore, is effective.

Finally, formulation 539-106 met both effectiveness criteria in this study. Comparing test formulation 607-41A to test formulation 607-20A demonstrates that 2% titanium dioxide contributes an SPF of 8. Comparing test formulation 607-20A with test formulation 607-12A shows that 2% ecamsule contributes an SPF of 6. Although the individual contributions of 10% octocrylene and 2% avobenzone cannot be determined in this study, the results for study PEN.810.05 demonstrate that these ingredients contribute SPFs greater than 2 in the same vehicle.

6.1.5 Clinical Microbiology

No antimicrobial claims are made. Therefore, this section is not applicable.

6.1.6 Efficacy Conclusions

A total of six studies were conducted to evaluate the effectiveness of formulations 760-006, 539-009, and 539-106 in protecting against UVB radiation. The test method derives from the sunscreen monograph (i.e., 21 CFR part 352 subpart D). The studies adequately demonstrate that all three formulations are effective in helping prevent sunburn by providing protection against UVB radiation.

Table 9. Labeled SPF Values for Formulation 760-006 (NDA 21-501)

Study	Labeled SPF	Number of subjects
PEN.810.05	17	24
PEN.810.06	17	23

A total of 47 evaluable subjects participated in two studies designed to demonstrate that formulation 760-006 is effective in protecting against UVB radiation. The submitted labeling for this formulation claims an SPF of 15. The data support this claim. The mean labeled SPF determined in both of these studies is 17.

Table 10. Labeled SPF Values for Formulation 539-009 (NDA 21-502)

Study	Labeled SPF	Number of subjects
PEN.810.01	15	21
PEN.810.02	16	20
PEN.810.05	17	24
PEN.810.06	15	25

A total of 90 evaluable subjects participated in four studies designed to demonstrate that formulation 539-009 is effective in protecting against UVB radiation. The submitted labeling for this formulation claims an SPF of 15. The data support this claim. The mean labeled SPF ranges from 15 to 17.

Table 11. Labeled SPF Values for Formulation 539-106 (NDA 21-471)

Study	Labeled SPF	Number of subjects
PEN.810.03	23	20
PEN.810.04	29	21
PEN.810.05	22	25
PEN.810.06	23	25

A total of 91 evaluable subjects participated in four studies designed to demonstrate that formulation 539-106 is effective in protecting against UVB radiation. The submitted labeling for this formulation claims an SPF of 20. The data support this claim. The mean labeled SPF determined in these four studies ranged from 22 to 29.

6.2 Indication

The sponsor makes a claim that the SPF values for two of the three sunscreen formulations (760-006 and 539-106) are valid under water resistant conditions, as defined in the OTC sunscreen drug monograph. According to the monograph, the labeled SPF values should be accurate following 40 minutes of water immersion (§ 352.52(b)(1)(ii)).

6.2.1 Methods

For sunscreen formulations making a claim of "water resistant," the SPF value is determined as described in section 6.1.1 except subjects are immersed in water (indoor fresh water pool, whirlpool, or jacuzzi) for 40 minutes following sunscreen application and prior to UV exposure (§ 352.76).

6.2.2 General Discussion of Endpoints

The endpoint in these studies is erythema. Refer to section 6.1.2 for further discussion.

6.2.3 Study Design

The same study design issues discussed in section 6.1.3 are applicable to these studies. As concluded in section 6.1.3, the study design is appropriate and acceptable for these studies.

6.2.4 Efficacy Findings

6.2.4.1 Study PEN.820.01

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on May 3, 2000, and concluded on June 15, 2000. A total of 21 evaluable subjects completed the study. Twenty of the subjects were female with an age range of 25 to 58 years (average age 43 years) and had skin type I, II, or III.

This study evaluates the effectiveness, following 40 minutes of water immersion, of formulations 760-006 (NDA 21-501) and 539-106 (NDA 21-471). In accordance with 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly. Additionally, each subject was treated with a "water resistant control" sunscreen (Coppertone® Waterproof Sunscreen SPF 15).

The principal investigator reports two minor deviations from the IRB-approved protocol. Subject #06 took ibuprofen for headache nine days prior to the study, and subject #11 took aspirin for a headache one day before the study. Because these exclusionary medications were only taken one-time, the principal investigator felt that these deviations did not affect the study results. This reviewer concurs.

The mean SPF ± SD of the 8% homosalate standard sunscreen was reported to be 4.64 ± 0.51. This SPF falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of the water resistant control sunscreen was 16.62 ± 2.10. The expected SPF of 15 falls within the 95% confidence interval of the calculated SPF. These results for the control sunscreens indicate that study results are valid.

The mean SPF ± SD of formulation 760-006 in this study was 16.93 ± 2.88. The 95% confidence interval ranged from 15.8 to 18.0, resulting in a labeled SPF of 15. The mean SPF ± SD of formulation 539-106 was 22.16 ± 2.84, with a 95% confidence interval of 21.1 to 23.3. The labeled SPF for formulation 539-106 was 21.

Both formulations 760-006 and 539-106 appear to be effective sunscreens following 40 minutes of water immersion. The two formulations meet the criteria specified in 21 CFR 352.20(a) that a formulation have an SPF value greater than 2 times the number of active ingredients. The contributions of individual active ingredients to the effectiveness of the finished products, as required by 21 CFR 352.20(a), were addressed in studies PEN.810.05 and PEN.810.06 under static (i.e., not water resistant) conditions. Because the SPF values for formulations 760-006 and 539-106 in this study were essentially identical to the values determined in studies PEN.810.05 and PEN.810.06, it can be assumed that each active ingredient contributes to the effectiveness of the final formulation under water resistant conditions as they did in studies PEN.810.05 and PEN.810.06.

6.2.4.2 Study PEN.820.02

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at CPTC in Fairfield, NJ. The study began on May 11 2000, and concluded on July 5, 2000. Twenty-five subjects were enrolled in the study. Fourteen of the enrolled subjects were female and 11 were male. All of the subjects had skin type I, II, or III. A total of 23 evaluable subjects completed the study for formulation 760-006, and 21 evaluable subjects completed the study for formulation 539-106.

This study evaluates the effectiveness, following 40 minutes of water immersion, of formulations 760-006 (NDA 21-501) and 539-106 (NDA 21-471). In accordance with 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly. Additionally, each subject was treated with a "water resistant control" sunscreen (Coppertone® Waterproof Sunscreen SPF 15).

The principal investigator reports 11 minor deviations from the IRB-approved protocol. Three subjects had MED readings made 1 hour or less outside the 22-24 hour post-irradiation period. Three subjects were screened and had preliminary irradiation on different days. Three subjects treated with formulation 539-106 were exposed to slightly lower doses of UV radiation than others in their test group, but a SPF value could still be accurately determined. Two subjects participated in a study requiring the application of topical antiperspirants within 6 weeks of the initiation of this study. The principal investigator felt that these deviations did not affect the study results. This reviewer concurs.

The mean SPF ± SD of the standard sunscreen was reported to be 4.50 ± 0.62. This SPF falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of the water resistant control sunscreen was 15.32 ± 2.10. The expected SPF of 15 falls within the 95% confidence interval of the calculated SPF. These results indicate that study results are valid.

The mean SPF ± SD of formulation 760-006 in this study was 16.47 ± 1.94. The 95% confidence interval ranged from 15.78 to 17.16, resulting in a labeled SPF of 15. The mean

SPF ± SD of formulation 539-106 was 24.31 ± 2.86, with a 95% confidence interval of 23.23 to 25.39. The labeled SPF for formulation 539-106 was 23.

Both formulations 760-006 and 539-106 appear to be effective sunscreens following 40 minutes of water immersion. The two formulations meet the criteria specified in 21 CFR 352.20(a) that a formulation have an SPF value greater than 2 times the number of active ingredients. The contributions of individual active ingredients to the effectiveness of the finished products, as required by 21 CFR 352.20(a), were addressed in studies PEN.810.05 and PEN.810.06 under static (i.e., not water resistant) conditions. Because the SPF values for formulations 760-006 and 539-106 in this study were essentially identical to the values determined in studies PEN.810.05 and PEN.810.06, it can be assumed that each active ingredient contributes to the effectiveness of the final formulation under water resistant conditions as they did in studies PEN.810.05 and PEN.810.06.

6.2.4.3 Study 99001.01.COS (80)

This phase 2/3 study was conducted under the supervision of Dr. Robert Shanahan at CPTC in Fairfield, NJ. The study began on December 14 1999, and concluded on January 22, 2000. Twenty-four subjects were enrolled in the study. Eighteen of the enrolled subjects were female, and six were male. All of the subjects had skin type I, II, or III. Twenty-one evaluable subjects completed the study. One enrolled subject was disqualified for taking an exclusionary medication (Ortho Tri-Cyclen birth control), and two subjects were disqualified because MEDs could not be determined over the range of radiation doses applied.

This study evaluated the effectiveness of formulation 760-006 (NDA 21-501) only. SPF values were determined both prior to water immersion (i.e., static SPF) and following 40 minutes of water immersion. In accordance with 21 CFR 352.70, an 8% homosalate standard sunscreen was tested concomitantly. Additionally, each subject was treated with a "water resistant control" sunscreen (Coppertone® Waterproof Sunscreen SPF 15).

The principal investigator reports 13 minor deviations from the IRB-approved protocol. Twelve subjects had post-irradiation erythema readings one hour or less outside the mandated 22-24 hour range. One subject participated in a Repeated Insult Patch Test (location of test site not provided) within six weeks prior to the initiation of this study. The principal investigator felt that these deviations did not affect the study results. Even if the test site for the patch test were on the subject's back, the SPF test method does not exclude subjects based on this criterion. Thus, this reviewer concurs that these deviations are not significant.

The mean SPF ± SD of the standard sunscreen was reported to be 4.83 ± 0.68. This SPF falls within the acceptable range specified in 21 CFR 352.70(a), which is 4.47 ± 1.279. The mean SPF ± SD of the water resistant control sunscreen was 16.04 ± 2.43. The expected SPF of 15

falls within the 95% confidence interval of the calculated SPF. These results indicate that the study results are valid.

The mean static SPF of formulation 760-006 in this study was 20.24 ± 2.54. The 95% confidence interval ranged from 19.08 to 21.39, resulting in a labeled SPF of 19. The mean post-immersion SPF of formulation 760-006 was 19.07 ± 2.75, with a 95% confidence interval of 17.82 to 20.32. The labeled water resistant SPF for formulation 760-006 was reported as 18. However, the correct labeled SPF is 17 (i.e., the largest whole number less than 17.82).

Formulation 760-006 is an effective sunscreen both before (SPF 19) and after water immersion (SPF 18). Because the sponsor claims that this formulation has a water resistant SPF of 15 the formulation meets that criterion. The formulation also meets the criteria specified in 21 CFR 352.20(a) requiring that a formulation have an SPF value greater than 2 times the number of active ingredients. The contributions of individual active ingredients to the effectiveness of the finished product, as required by 21 CFR 352.20(a), was addressed in studies PEN.810.05 and PEN.810.06 under static (i.e., not water resistant) conditions. Because the SPF values for formulation 760-006 were essentially identical under static and water resistant conditions, it can be assumed that each active ingredient contributes to the effectiveness of the final formulation under water resistant conditions as they did in studies PEN.810.05 and PEN.810.06.

6.2.5 Clinical Microbiology

No antimicrobial claims are made. Therefore, this section is not applicable.

6.2.6 Efficacy Conclusions

Three separate studies were conducted to evaluate the effectiveness of formulations 760-006 (NDA 21-501) and 539-106 (NDA 21-471) in protecting against UVB radiation following 40 minutes of water immersion. The methodology followed that outlined in 21 CFR part 352 subpart D. The studies adequately demonstrate that both formulations are effective in helping prevent sunburn by providing protection against UVB radiation after 40 minutes of water immersion.

Table 12. Water Resistant SPF Values for Formulation 760-006 (NDA 21-501)

Study	WR[1] SPF	Number of subjects
PEN.820.01	15	21
PEN.820.02	15	23
99001.01.COS	18	21

[1] WR denotes water resistant.

A total of 65 evaluable subjects participated in three studies designed to demonstrate that formulation 760-006 provides effective protection against UVB radiation following 40 minutes of water immersion. The sponsor makes the claim that formulation 760-006 has a water resistant SPF of 15. The data support this claim. The labeled SPF determined in these three studies equaled or exceeded 15.

Table 13. Water Resistant SPF Values for Formulation 539-106 (NDA 21-471)

Study	WR[1] SPF	Number of subjects
PEN.820.01	21	21
PEN.820.02	23	23

[1] WR denotes water resistant

A total of 44 evaluable subjects participated in two studies designed to demonstrate that formulation 539-106 is effective in protecting against UVB radiation following 40 minutes of water immersion. The sponsor makes the claim that formulation 539-106 has a water resistant SPF of 20. The data support this claim. The labeled SPF determined in these two studies exceeded 20.

6.3 Indication

The proposed labeling for the three formulations includes claims regarding protection against UVA radiation. The labeling includes PFA values. A UVA claim of "broad spectrum protection" is allowed for OTC sunscreens marketed under the sunscreen monograph, but PFA values are not currently allowed (*Federal Register* vol. 64, p. 27672).

6.3.1 Methods

FDA has not yet published a final rule specifying testing procedures for evaluating the UVA radiation protection of sunscreens. In the 1993 TFM for OTC sunscreen drug products, FDA states that a sunscreen can bear a claim that it provides UVA protection if it meets two criteria (58 FR 28194 at 28233):

- the absorption spectrum extends to 360 nm or above in the UVA range
- UVA protection is demonstrated using an appropriate testing procedure

In the same document, FDA states that we believe a testing method similar to the one described by Lowe et al. (Ref. 1) could be used to demonstrate that a sunscreen provides protection against UVA radiation (58 FR 28194 at 28250). A 1996 amendment to the TFM reaffirms FDA's belief that the method of Lowe et al. is an appropriate test. In addition, FDA stated that the testing procedure described by Gange et al. (Ref. 2) is adequate (61 FR 48645 at 48652). The methods described by Lowe et al. and Gange et al. are similar to each other. In a 1998 amendment to the TFM, FDA found a third testing procedure to be adequate for evaluating UVA protection. This method is based on determination of a minimal response dose (MRD) and is similar to the SPF

test method except that the endpoint (i.e., "response") is pigment darkening rather than erythema (63 FR 56584 at 56587).

The sponsor submitted results from UVA effectiveness studies conducted according to two test methods:

(1) the persistent pigment darkening (PPD) method
(2) a method similar to the methods of Lowe et al. and Gange et al.

The PPD method used in studies PEN.910.01 and PEN.910.02 is nearly identical to the MRD testing method. According to the MRD method, each subject is exposed to increasing amounts of simulated solar radiation in the absence or presence of a sunscreen. The MRD for protected and unprotected skin is determined for each subject. MRD represents the lowest radiation dose that causes pigment darkening that lasts 22-24 hours, because UVA radiation primarily causes the skin to darken (rather than redden). The protection factor for UVA, termed PFA, is then calculated as the ratio of MRD (protected skin) to MRD (unprotected skin). Thus, UVA protection increases with increasing PFA. A minimum of 20 subjects are required to complete the study according to the MRD protocol identified as acceptable by FDA (63 FR 56584 at 56587). As with the SPF test method, a sunscreen standard is tested concurrently to validate the study results.

The 8-methoxypsoralen (8-MOP) method was used in Study PEN.920.01. According to this method, an alcohol solution containing 0.1% 8-MOP is applied to the skin of each subject. The 8-MOP photosensitizes the skin to UVA radiation, such that UVA radiation produces erythema instead of pigment darkening. Approximately 45 minutes after application of 8-MOP, each subject is irradiated with increasing doses of UVA radiation. Seventy-two hours post-irradiation, the skin is evaluated for erythema to determine a minimal phototoxic dose (MPD).

After determining the MPD for each subject, a phototoxic protection factor (PPF) is identified for different sunscreen formulations. The PPF is calculated as the ratio of MPD (protected skin) to MPD (unprotected skin). Thus, a larger PPF represents greater protection against UVA radiation. The number of subjects required in 8-MOP studies varies. Lowe et al. enrolled 26 subjects in each study (Ref. 1), whereas Gange et al. enrolled 41 (Ref. 2).

6.3.2 General Discussion of Endpoints

The endpoints according to the two UVA protection methods differ. The PPD (MRD) method utilizes pigment darkening, whereas the 8-MOP method utilizes erythema. According both methods, the endpoints are used to calculate protection factors. Both PFA and PPF values reflect the degree of UVA radiation provided by a sunscreen. Therefore, for consistency, the sponsor defines protection against UVA radiation using the term PFA for all UVA protection studies.

6.3.3 Study Design

These studies were designed in accordance with FDA's published comments regarding UVA protection. As stated in the 1998 TFM, until we propose a UVA protection test method, FDA

"considers testing procedures similar to the UVA protection factor method...and those methods described by R.W. Gange et al. and N.J. Lowe et al. as adequate for determining the UVA protection potential of a finished OTC sunscreen drug product" (63 FR 56584 at 56587). Inclusion and exclusion criteria are as defined in these methods. The submitted studies conform to these methods except where noted below. In general, the inclusion and exclusion criteria are similar to those of the SPF test. The only significant difference concerns the skin types of study subjects. The SPF test method requires skin types I, II, and III. The PPD method utilizes skin types II, III, and IV, which allow pigment darkening (rather than erythema).

6.3.4 Efficacy Findings

Three studies were submitted to support a claim of effectiveness in protecting against UVA radiation. The three studies determined protection factors (PFA values) for formulations 760-006, 539-009, and 539-106. This review first discusses the two studies conducted according to the PPD/MRD method (PEN.910.01 and PEN.910.02) and then the study conducted according to the 8-MOP method (PEN.920.01).

6.3.4.1 Study PEN.910.01

This phase 3 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on September 31, 2000, and concluded on October 10, 2000. Thirty-two subjects enrolled in the study. Seventeen of the enrolled subjects were female, and fifteen were male. The subjects ranged in age from 18 to 65 years (average age 41.7 years) and had skin type II, III, or IV. A total of 30 evaluable subjects completed the study.

This study evaluates the effectiveness of formulations 760-006, 539-009, and 539-106 in protecting against UVA radiation. In this study, the standard sunscreen was the JCIA 2 UVA Standard, with an expected PFA value of 3.75.

The principal investigator reports minor deviations for all subjects. Each subject had one of the test products and the UVA control product applied randomly to two sites rather than the protocol-specified randomized application of all 3 test products and the UVA control product to four sites. This resulted in only ten subjects being evaluated for each test formulation rather than required 20 subjects. Because the variation about the mean PFA values is relatively small, this reviewer does not consider the protocol deviation to have substantially affected the study results. Even though these deviations may decrease the accuracy of the PFA values, as discussed below, this review only evaluates the UVA studies to determine whether the formulations are effective (not the level of effectiveness).

The mean PFA ± SD for each test formulation and concurrently run standard sunscreen are presented in the table below.

Table 14. PFA Values for Different Formulations Tested in Study PEN.910.01

Test Formulation	Mean PFA ± SD	Standard Mean PFA ± SD
760-006	21.70 ± 3.77	4.29 ± 0.92
539-009	19.53 ± 3.39	4.05 ± 0.59
539-106	26.24 ±2.64	4.48 ± 1.10

The expected PFA of 3.75 falls within the 95% confidence interval of the PFA for the standard sunscreen in each trial. These results for the standard indicate that study results are valid. The mean PFA ± SD of formulation 760-006 is 21.70 ± 3.77. The mean PFA ± SD of formulation 539-009 is 19.53 ± 3.39. The mean PFA ± SD of formulation 539-106 is 26.24 ± 2.64.

Although PFA values are given, FDA has not yet established a rating scale for UVA protection in the OTC sunscreen monograph. Therefore, this review only evaluates the UVA studies to determine whether the sunscreen formulations are effective UVA protectants (not the degree of UVA protection). Because PFA values are calculated in a manner analogous to SPF values, this reviewer is evaluating effectiveness in UVA protection based on the effectiveness criteria for UVB protection (21 CFR 352.20(a)). Thus, the final formulation is found to provide effective UVA protection if the PFA equals or exceeds two times the number of active ingredients. This reviewer does not think that the formulations need to meet the second criterion for UVB protection effectiveness (i.e., each active ingredient contributes a PFA of at least two to the final formulation). This criterion is included in the OTC sunscreen monograph for SPF determinations because sunscreen product labeling attributes UVB protection (i.e., sunburn protection) to each active ingredient. In contrast, a general UVA protection claim of "broad spectrum" does not specify which active ingredients are contributing to effective UVA protection. Thus, not every active ingredient must contribute to UVA radiation protection.

The PFAs of all three formulations greatly exceed two times the number of active ingredients. Thus, the sunscreens provide effective UVA protection in both women and men, and it is expected that the formulations will also be effective on children (over 6 months of age).

6.3.4.2 Study PEN.910.02

This phase 2 study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on June 26, 2002, and concluded on July 26, 2002. Seventy evaluable subjects completed the study. Forty of the enrolled subjects were female, and thirty were male. The subjects ranged in age from 18 to 62 years (average age 34.7 years) and had skin type III or IV. Each subject was randomly assigned one test formulation and the standard sunscreen, such that each of seven test products was tested on 10 subjects.

This study was designed to evaluate the effectiveness of seven test formulations containing various combinations of active ingredients in formulations 760-006, 539-009, and 539-106. These are the same test formulations evaluated for UVB protection in Study — 810.06. The JCIA 2 UVA standard sunscreen was evaluated concurrently.

Table 15. Composition of Test Formulations in Study — .910.02

Test Formulation	10% Octocrylene			2% Avobenzone	2% Ecamsule	3% Ecamsule	2% Titanium dixoide
607-76A	✓			✓			✓
607-12A	✓			✓			
607-20A	✓			✓	✓		
607-27A (539-009)	✓			✓	✓		
607-34A (760-006)	✓			✓		✓	
607-41A (539-106)	✓			✓	✓		✓
607-67A	✓			✓			

b(4)

The principal investigator reports four deviations from the IRB-approved protocol:

- The MRD for subject 16/ — was determined less than two hours after irradiation (rather than the required 3 ± 1 hour post-irradiation).
- Evaluators differed on successive days for three subjects (2/ — 29 —, and 66/ —

b(6)

This reviewer agrees with the principal investigator that these deviations do not interfere with the study results.

The expected PFA of 3.75 falls within the 95% confidence interval of the PFA for the standard sunscreen in each trial. These results for the standard indicate that study results are valid. The mean PFA ± SD for each test product and concurrently run standard sunscreen are presented in the table below.

Table 16. PFA Values for Different Formulations Tested in Study — 910.02

Test Formulation	Mean PFA ± SD	Standard Mean PFA± SD
607-76A	12.85 ± 3.02	3.96 ± 0.55
607-12A	8.25 ± 2.13	4.57 ± 0.96
607-20A	12.05 ± 2.84	4.45 ± 0.86
607-27A (539-009)	15.84 ± 3.34	4.34 ± 0.71
607-34A (760-006)	22.19 ± 5.99	4.07 ± 0.80
607-41A (539-106)	18.46 ± 3.61	3.90 ± 0.74
607-67A	6.75 ± 0.96	3.86 ± 0.49

This study demonstrates that the three formulations provide effective protection against UVA radiation. The formulations produced PFA values ranging from 15.84 (539-009) to 22.19 (760-006). In addition, this study demonstrates the effectiveness of each active ingredient contained in formulations 760-006, 539-009, and 539-106. For example, comparing the PFA value for formulation 607-27A (539-106) with the PFA value for formulation 607-20A shows that 2% ecamsule provides a PFA value of 3. Comparing formulation 607-20A with formulation 607-12A demonstrates that 2% avobenzone contributes a PFA value of 4 to the PFA of the formulation 539-106. Likewise, comparing formulation 607-34A (760-006) with formulation 607-12A shows that the inclusion of 3% ecamsule increases the formulation PFA value by 14. Finally, comparing formulation 607-41A (539-106) with formulation 607-20A shows that 2% titanium dioxide contributes a PFA value of 6 to the PFA of formulation 539-106.

— does not appear to contribute to protection against UVA radiation. The — does not have a consistent effect on PFA values. Test formulation 607-12A, which includes the — produced a PFA value of 8, whereas the same formulation without the — i.e., 607-67A) produced a PFA value of 6. In contrast, test formulation 607-27A, which includes the — produced a PFA value of 12, whereas the same formulation without the — i.e., 607-27A) produced a PFA value of 15. Thus, the — decreased the PFA value by 2 in one formulation and increased the PFA value by 3 in the other formulation. b(4)

This study does not provide information about the possible contribution of 10% octocrylene to the formulation PFA values. Octocrylene would not be expected to provide protection against UVA radiation because the ingredient absorbs light almost exclusively in the UVB region of the spectrum.

6.3.4.3 Study PEN.920.01

This phase 3 study was conducted under the supervision of Dr. Alan H. Greenspan at TKL Research Inc. in Paramus, NJ. The study began on September 27, 2000, and concluded on October 12, 2000. A total of 14 subjects enrolled in the study. Twelve of the subjects were female, and two were male. The age range of the subjects was 35 to 65 years (average age 46.5 years), and subjects had skin type II or III. Ten subjects were evaluable for formulation 760-006. Eleven subjects were evaluable for formulation 539-009. Twelve subjects were evaluable for formulation 539-106. The number of subjects included in this study is considerably lower than the number of subjects included in the studies by Lowe et al. (Ref. 1) and Gange et al. (Ref. 2).

This study evaluates the effectiveness of formulations 760-006, 539-009 , and 539-106 in protecting against UVA radiation using the 8-MOP method (Refs. 1 and 2). No standard sunscreen preparation was utilized. Effectiveness was measured against untreated (control) sites.

The principal investigator reports nine minor deviations from the IRB-approved protocol. Four subjects had different evaluators assess MPDs on different test days. Four subjects took exclusionary medications (approved by the sponsor). One subject was inadvertently exposed to slightly higher doses of UVA radiation than others in his test group. This reviewer concurs with the principal investigator that these deviations are not likely to affect the study results.

The mean PFA values ± SD for each of the three test products are presented below.

Table 17. PFA Values for Different Formulations Tested in Study PEN.920.01

Test Formulation	Mean PFA ± SD
760-006	26.96 ± 9.43
539-009	27.65 ± 10.91
539-106	29.17 ± 7.76

In the absence of a concomitantly run standard, it is not possible to validate these results. Furthermore, the numbers of subjects tested with each formulation is low compared with the numbers enrolled in the two reference studies. Because of the low enrollment, the standard deviation values are high (greater than 25% of the mean values). The PFA values calculated using the 8-MOP method in this study are consistently higher than but comparable to the PFA values calculated using the PPD method (Study PEN.910.01). The mean PFA value for formulation 539-106 is higher than the mean PFA values of formulations 760-006 and 539-009, and the mean PFA values for formulations 760-006 and 539-009 are very similar.

Even though there is substantial variation about the mean PFA values calculated in this study, the PFA values are clearly greater than two times the number of active ingredients in each formulation. Thus, this study supports the effectiveness of the three formulations in protecting against UVA radiation.

6.3.5 Clinical Microbiology

No antimicrobial claims are made. This section is not applicable.

6.3.6 Efficacy Conclusions

A total of three clinical studies were conducted to demonstrate that formulations 760-006, 539-009, and 539-106 effectively protect against UVA radiation. Two studies were conducted using the PPD method (Studies PEN.910.01 and PEN.910.02). This method is comparable to the MRD method previously cited by FDA as acceptable (63 FR 56584 at 56587). The other study was conducted using the 8-MOP method, which is comparable to the FDA-accepted methods of Lowe et al. (Ref. 1) and Gange et al. (Ref. 2). In all three studies, UVA protection is defined by a PFA value, which is analogous to an SPF value for UVB protection. The three formulations appear to be effective in providing protection against UVA radiation.

Table 18. Mean PFA Values for Each Sunscreen Formulation

Study	760-006 (NDA 21-501)	539-009 (NDA 21-502)	539-106 (NDA 21-471)
PEN.910.01	21.70	19.53	26.24
PEN.910.02	22.19	15.84	18.46
PEN.920.01	26.96	27.65	29.17

A total of 110 evaluable subjects participated in the three clinical studies. PFA values are comparable in the PPD (PEN.910.01 and PEN.910.02) and 8-MOP studies (PEN.920.01). The submitted data support the claim that each of these sunscreen formulations protects against UVA radiation. Formulation 539-106 seems to provide the greatest amount of protection, with mean PFA values ranging from 18.46 to 29.17. Formulations 760-006 and 539-009 also seem to be effective, with mean PFA values greater than 21 and 15, respectively.

Because PFA values are calculated in a manner analogous to SPF values, this reviewer is determining UVA protection effectiveness based on the effectiveness criteria for UVB protection (21 CFR 352.20(a)). Thus, the final formulation is found to provide effective UVA protection if the PFA equals or exceeds two times the number of active ingredients. This reviewer does not think that the formulations need to meet the second criterion for UVA protection effectiveness (i.e., each active ingredient contributes a PFA of at least two to the final formulation). This criterion is included in the OTC sunscreen monograph because sunscreen product labeling attributes UVB protection (i.e., sunburn protection) to each active ingredient. In contrast, a

6.4.3 Study Design

The critical wavelength is useful in determining the ability of a sunscreen to absorb long-wavelength UVA radiation, as a longer critical wavelength implies greater protection against long-wavelength UVA radiation (i.e., $\geq$ 360 nm). Although the studies use synthetic human skin, the results can be extrapolated to human use. The absorption spectra will be different on different skin types, so it is impossible to determine a single spectrum for all consumers under actual use conditions. Rather, synthetic human skin can be expected to provide an approximation of the spectrum under OTC use conditions.

6.4.4 Efficacy Findings

6.4.4.1 Study S01-0205

This in vitro study was conducted under the supervision of Dr. Robert Shanahan at the CPTC in Fairfield, NJ. The study began on April 10, 2001, and concluded on April 11, 2001.

Critical wavelengths for each of the three test formulations are presented in the table below.

Table 21. Mean Critical Wavelengths for Different Formulations Tested in Study S01-0205

Test Formulation	Mean Critical Wavelength (nm)
760-006	381
539-009	378
539-106	382

All three formulations exhibited critical wavelengths of approximately 380 nm. Therefore, the formulations meet the criterion of protecting against UVA radiation $\geq$ 360 nm.

6.4.4.2 Study D20041030

This in vitro study was conducted by Mlle Marjorie Boudet at the L'Oreal Laboratory in Chevilly-Larue, France. The study involved the same formulations included in studies PEN.810.06 and PEN.910.02.

Critical wavelengths for each of the three test formulations that are the subject of this review are presented in the table below.

Table 21. Mean Critical Wavelengths for NDA Formulations Tested in Study D20041030

Test Formulation	Mean Critical Wavelength (nm)
607-27A (539-009)	380
607-34A (760-006)	379
607-41A (539-106)	380

All three formulations exhibited critical wavelengths of approximately 380 nm. Therefore, the formulations meet the criterion of protecting against UVA radiation ≥ 360 nm.

6.4.4.3 Study SOL-DP1-97-021

This in vitro study was conducted by M. Joel Bover at the L'Oreal Laboratory in Clichy, France. The study included several formulations. Two of the formulations are subjects of this review. Critical wavelengths for the two formulations are presented in the table below.

Table 22. Mean Critical Wavelengths for Formulations 427923 and 427928 in Study SOL-DP1-97-021

Test Formulation	Mean Critical Wavelength (nm)
427923 (760-006)	379
427928 (539-106)	382

Both formulations exhibited critical wavelengths of approximately 380 nm. Therefore, the formulations meet the criterion of protecting against UVA radiation ≥ 360 nm.

6.4.5 Clinical Microbiology

No antimicrobial claims are made. This section is not applicable.

6.4.6 Efficacy Conclusions

All three formulations effectively absorb UV light at wavelengths ≥ 360 nm. Thus, all three formulations meet both criteria specified in the 1993 tentative final monograph (TFM) for OTC sunscreen drug products. The formulations may bear UVA protection claims such as the following (58 FR 28194 at 28233):

- "broad spectrum"
- "protects against UVA rays or radiation"

7 INTEGRATED REVIEW OF SAFETY

The safety of the three formulations is being evaluated separately by reviewers in the Office of Nonprescription Products and the Division of Dermatological and Dental Drug Products.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing directions for the SPF 15 and SPF 20 WR sunscreen lotions (NDAs 21-501 and 21-471) are as follows:

- apply liberally 15 minutes before sun exposure
- reapply as needed or after towel drying, swimming, or perspiring
- children under 6 months of age: ask a doctor

The proposed dosing directions for the SPF 15 sunscreen lotion are as follows:

- apply evenly to cleansed skin before sun exposure and as needed
- children under 6 months of age: ask a doctor

The proposed dosing directions are consistent with the OTC sunscreen drug monograph (21 CFR part 352).

8.2 Drug-Drug Interactions

Potential drug-drug interactions are discussed as part of the safety review conducted by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

8.3 Special Populations

There are no special populations related to effectiveness. Special populations related to safety are discussed as part of the safety review conducted by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

8.4 Pediatrics

These formulations are effective for children older than 6 months of age. This is consistent with the OTC sunscreen drug monograph (21 CFR part 352). The safety of the formulations for children is pending evaluation by reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

8.5 Advisory Committee Meeting

No advisory committee meeting is necessary to evaluate effectiveness of the three formulations.

8.6 Literature Review

A literature review was conducted as part of the safety review by Daiva Shetty, M.D., in the Office of Nonprescription Products.

8.7 Postmarketing Risk Management Plan

The need for a postmarketing risk management plan is pending safety evaluation by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products.

8.8 Other Relevant Materials

There are no other relevant materials submitted for review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The effectiveness of the three sunscreen formulations containing ecamsule in combination with other GRASE sunscreen active ingredients is acceptable for OTC marketing. The formulations provide effective protection against UVB and UVA radiation. The formulations in NDAs 21-501 and 21-471 are effective after 40 minutes of water immersion. However, the effectiveness of the formulation in NDA 21-502 after traveling through the pump dispenser is unknown. It is highly likely that the pump does not alter the efficacy of the formulation, but the sponsor needs to conduct an SPF test to demonstrate that the pump does not lower efficacy.

9.2 Recommendation on Regulatory Action

b(4)

Based on effectiveness, the following sunscreens should be approved for over-the-counter (OTC) use for prevention of ——— nduced by UVB and UVA radiation:

- SPF 15 water resistant sunscreen lotion
- SPF 15 sunscreen lotion
- SPF 20 water resistant sunscreen lotion

Final approvability depends on the outcome of the preclinical and clinical safety and chemistry studies being evaluated by other reviewers.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

This review only considers the effectiveness of the three formulations in NDAs 21-501, 21-502, and 21-471. Therefore, this section is not applicable.

9.3.2 Required Phase 4 Commitments

There are no required phase 4 commitments with respect to efficacy..

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Evaluation of the proposed labeling is being done in a separate review.

9.5 Comments to Applicant

This review does not have any comments to convey to the applicant.

10 APPENDICES

No appendices are included.

REFERENCES

1. Lowe et al., "Indoor and outdoor efficacy testing of broad spectrum sunscreen against UVA radiation in psoralin-sensitized subjects," J. Am. Acad. Dermatol. 17:224-230, 1987.
2. Gange R.W. et al., "Efficacy of a sunscreen containing butyl methoxydibenzoylmethane against ultraviolet A radiation in photosensitized subjects," J. Am. Acad. Dermatol. 15:494-499, 1986.

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Michael Koenig
1/6/2006 02:29:54 PM
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Matthew has reviewed and OKed edits

Charles Ganley
1/9/2006 08:14:10 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-501
Submission Code	N-000
Letter Date	May 16, 2005
Stamp Date	May 16, 2005
PDUFA Goal Date	March 16, 2006
Reviewer Name	Phyllis A. Huene, M.D.
Review Completion Date	October 17, 2005
Established Names	Ecamsule, Avobenzone, Octocrylene
(Proposed) Trade Name	(b) (4) SPF 15 Water Resistant Sunscreen Lotion
Therapeutic Class	Sunscreen agent
Priority Designation	S
Formulation	Lotion
Dosing Regimen	Application 15 minutes before sun exposure
Indication	Sun protection
Intended Population	age 6 months and older

MEDICAL OFFICER'S REVIEW OF NDA 21-501
ORIGINAL SUBMISSION

SPONSOR: L'Oreal USA Products, Inc.

PRODUCT: NDA 21-501: (b) (4) SPF 15 Water Resistant Sunscreen Lotion (760-006)

Active ingredients: ecamsule* 3%, avobenzone 2%, octocrylene 10%.

*Trade name for ecamsule is Mexoryl SX.

MATERIAL REVIEWED: Phase 1 studies. The other portions of the NDA submissions are to be reviewed by the Division of OTC Drug Products.

REVIEWER'S EVALUATION OF PHASE 1 STUDIES: The dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. There is some potential for sensitization. The comedogenicity study is not adequate to conclude that the product is not acnegenic or comedogenic.

Study PEN 110.01: Irritation and contact sensitization

This study was conducted at the facilities of Product Investigations, Inc., at its sites at Conshohocken, PA and Modesto, CA. The investigators were Morris Shelanski, M.D., at the former site and Daniel Trozak, M.D., at the latter site.

It was performed on 223 adult subjects, of which 217 subjects completed the study. Six subjects discontinued for non-related reasons and one was lost to followup.

The test products were (b) (4) formula 760-006, the subject of the current application, (b) (4) formula 539-106, the subject of pending NDA 21-471, and (b) (4) formula 539-009, the subject of pending NDA 21-502, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene	Titanium dioxide
760-006 (cream)	3%	2%	10%	-
539-009 (lotion)	2%	2%	10%	-
539-106 (cream)	2%	2%	10%	2%
White petrolatum	-	-	-	-

The patching devices were 8 mm diameter flexible Finn Chambers centered on a measured strip of (b) (4) tape, making an occlusive patch. Approximately 0.15 ml of the test materials were applied to the patches immediately prior to application. The patches were randomly applied to the test sites, and the investigator was blinded to the identification of the test products.

During the induction phase, applications were made to the same skin sites on the back, five times a week for three weeks. The patches were applied for a period of 24 hours on Mondays through Thursdays, and for 72 hours on Fridays, remaining in place until Monday. Skin reactions were evaluated immediately after patch removal. If a score of 3 or greater occurred at a patch site, an alternate skin site was used for subsequent applications.

After a rest period of one week, occlusive challenge applications were made to naive skin sites for 48 hours. Skin reactions were graded at patch removal and at 24 and 48 hours later. At one center the subjects were to be evaluated at day 8 if there were an equivocal reaction at 48 hours, while at the other center all subjects were evaluated at day 8.

Reactions were scored on the following scale:

0	No visible skin reaction
1	Redness, faint to moderate, with partial involvement of exposure area
2	Redness, moderate to intense, with total involvement of exposure area
3	Redness, intense, all of contact area involved
4	Redness, moderate to intense, plus edema or papules
5	Redness, moderate to intense, plus vesicles, blisters, or bullae
6	Redness, infiltration, plus extension of effect beyond area of contact

Other local reactions were recorded as follows.

0	Edema	Definite swelling
P	Papules	Many small, red, solid elevations; surface of reaction has granular feel
V	Vesiculation	Small (<0.5 cm) circumscribed elevations having translucent surfaces so that fluid is visible
B	Blisters	Bullae; large (>0.5 cm) circumscribed elevations with visible fluid
Pu	Pustules	Inflammatory small elevations containing yellow-white exudates
H	Hyperpigmentation	An increase of the usual pigmentation limited on the patch test area
W	Weeping/oozing	May be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting
S	Spreading of reaction beyond patch site	Reaction where no product came in contact with the skin.
Se	Superficial erosion	Slight to moderate removal of epidermis

Other skin reactions such as dryness, cracking, peeling, were noted as comments.

At the end of the challenge phase the investigators assessed the occurrence of possible contact sensitization as negative, equivocal, or positive. Signs and symptoms such as pruritus, vesicles, spreading or crescendo reactions were considered as possibly positive reactions. Any subject whose reaction was judged as equivocal at challenge was to be re-challenged after a two week rest period.

Results were as follows.

Of the 223 subjects enrolled, 6 subjects were discontinued from the study. Five subjects discontinued for non-medical reasons, and 1 subject was lost to followup. Analyses were conducted on 218 subjects.

1) Induction phase: Skin irritation was found in 3 subjects during the induction phase.

   One subject had grade 1 reactions on the first day of week 2 at the three test product sites, which subsequently increased to grade 4 reactions during week 2. At the start of week 3, three alternate

sites were patched, and at the end of week 3 the subject had grade 1-2 reactions to the three test products at the new test sites, and the original sites continued to show grade 4 reactions. No reactions were seen at the control site. The investigator concluded that the subject had entered the study pre-sensitized to the test products, and the subject was discontinued from the study.

Two subjects had grade 4 reactions, both at the (b) (4) lotion (539-009) sites, one on the fourth day of week 2 and one at the last application on the first day of week 4. The first subject was patched at an alternate site during week 3, and no further reactions occurred. The second subject showed grade 1 reactions during the next two days. The two subjects had also shown transient grade 1 reactions to the cream test products. Both subjects completed the study, and neither showed sensitization during the challenge phase.

The Mean Cumulative Irritancy Index for all three test products was 0.01.

2) Challenge phase: There were no reactions in any subjects to any of the test products.

Reviewer's evaluation: This study was adequately designed and executed, except that the usual requirement for a cumulative irritation study is that it be of 21 days duration. However, based on the results in the induction phase under conditions of exaggerated exposure, the test products would be expected to have little potential for irritation under conditions of normal use. No sensitization or other reactions were found in the challenge phase; however, one subject was apparently sensitized to the test products prior to initiation of the study. There is therefore some potential for sensitization with the test product.

Study PEN.210.01 - Photosensitization

The investigator for this study was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The subject population was 106 evaluable subjects.

The test products were (b) (4) formula 539-106, the subject of pending NDA 21-471, (b) (4) formula 539-009, the subject of pending NDA 21-502, and (b) (4) formula 760-006, the subject of the current application, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene	Titanium dioxide
760-006 (cream)	3%	2%	10%	-
539-009 (lotion)	2%	2%	10%	-
539-106 (cream)	2%	2%	10%	2%
White petrolatum	-	-	-	-

The light sources used were a UVA radiation source and a full spectrum radiation source. The UVA radiation source was a xenon arc solar simulator, filtered to remove radiation below 320 nm. The full spectrum radiation source was a xenon arc solar simulator with a continuous emission spectrum in the UVA and UVB range from 290 to 400 nm.

The minimal erythema dose (MED) of full spectrum radiation was determined for each subject prior to test applications. During the induction phase, 0.2 ml of the test products were applied under occlusive patches to skin sites on the back for 24 hours, twice weekly on Mondays and Thursdays, for 3 weeks. At each patch removal the sites were irradiated with 2 MEDs of full spectrum irradiation during the first week and with 3 MEDs during the second and third weeks. An untreated control site was included. Skin reactions were assessed at 30 minutes after patch removal, prior to irradiation.

The induction period was followed by a two week rest period. In the challenge phase, two sets of the test products were applied to naive skin sites under occlusion for 24 hours. After patch removal one set of sites was irradiated with 10 J/cm^2 of UVA irradiation followed by 0.8 MED of full spectrum radiation. The other set of sites served as treated, non-irradiated controls. An untreated control site was also included. Skin reactions were scored before irradiation, and at 48 and 72 hours after irradiation. A 96 hour evaluation was to be done if reactions were equivocal.

The following scale was used for grading reactions during the induction and challenge phases.

0	No visible skin reaction
0.5	Barely perceptible or spotty erythema
1	Mild erythema
2	Moderate erythema, possible presence of edema
3	Marked erythema, possible edema
4	Severe erythema, possible, edema, vesiculation, bullae and/or ulceration

Other local reactions were recorded as follows.

0	Edema	Definite swelling
P	Papules	Many small, red, solid elevations; surface of reaction has granular feel
V	Vesiculation	Small (<0.5 cm) circumscribed elevations having translucent surfaces so that fluid is visible
B	Blisters	Bullae; large (>0.5 cm) circumscribed elevations with visible fluid
Pu	Pustules	Inflammatory small elevations containing yellow-white exudates
H	Hyperpigmentation	An increase of the usual pigmentation limited on the patch test area
W	Weeping/oozing	May be a sign of vesiculation or blisters (epidermal damage) and manifest as crusting
S	Spreading of reaction beyond patch site	Reaction where no product came in contact with the skin.
Se	Superficial erosion	Slight to moderate removal of epidermis

Other skin reactions such as dryness, cracking, peeling, were noted as comments.

Immediate skin responses to irradiation consisting of tanning, reddening, or heat were evaluated as present or absent, using the following definitions.

Tanning: immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, attributed to photo-oxidation of existing melanin granules.

Reddening: immediate reddening, fading rapidly and viewed as a normal response of capillaries and venules to heat, and visible and IR radiation.

Heat response: immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating the skin surface.

Results were as follows.

137 subjects were enrolled into the study, of which 106 were evaluable for photosensitization reactions. The following subjects were discontinued from the study: 14 subjects were enrolled into another study concurrently or within 30 days of the start of this study; 4 subjects were taking an exclusionary medication; 2 subjects had disqualifying medical conditions; 1 subject was over the age limit of 65 years, and 11 subjects were discontinued at their request.

During the induction phase, erythema was seen in about 25% of the active product sites and in over 80% of the petrolatum sites during the third week. There were no reactions in the challenge phase.

Reviewer's evaluation: This study was adequately designed and executed. No sensitization or other reactions were found in the challenge phase, and the products would be expected to have little or no potential for photosensitization.

Study PEN.250.01 - Phototoxicity

The investigator for this study was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The subject population was 26 evaluable subjects.

The test products were (b) (4) formula 539-106, the subject of pending NDA 21-471, (b) (4) formula 539-009, the subject of pending NDA 21-502, and (b) (4) formula 760-006, the subject of the current application, and petrolatum as a control. The active ingredients were as follows.

Formulation	Ecamsule	Avobenzone	Octocrylene	Titanium dioxide
760-006 (cream)	3%	2%	10%	-
539-009 (lotion)	2%	2%	10%	-
539-106 (cream)	2%	2%	10%	2%
White petrolatum	-	-	-	-

The light source was a xenon arc solar simulator for full spectrum radiation, which was filtered to produce UVA radiation.

The minimal erythema dose (MED) of full spectrum radiation was determined for each subject prior to test applications. 0.2 ml of the test products were applied in two sets of occlusive patches to skin sites on the back for 24 hours. Two additional sites were untreated and occluded to serve as controls. At 60 minutes after patch removal, one set of test sites were irradiated with 20 Joules/cm^2 of UVA light, and were then exposed to 0.8 MED of full spectrum radiation. The patches were evaluated for reactions immediately following irradiation and at 24 and 48 hours later.

The following scale was used to grade erythema reactions.

0	No visible skin reaction
0.5	Barely perceptible or spotty erythema
1	Mild erythema
2	Moderate erythema, possible presence of edema
3	Marked erythema, possible edema
4	Severe erythema, possible, edema, vesiculation, bullae and/or ulceration

If any other local reactions were found, they were to be noted as in the photosensitization study.

Results were as follows.

26 subjects were enrolled into, and completed the study. There were no erythema or local reactions observed for any of the subjects at any observation time. The investigator concluded that no phototoxic reactions had occurred.

Reviewer's evaluation: This study was adequately designed and executed, except that the Agency generally requires 30 evaluable subjects in a phototoxicity study. No reactions were found after irradiation, and the products would be expected to have little or no potential for phototoxicity.

Study PEN.570.01 - Acnegenicity/Comedogenicity

This study was done on a related product, (b) (4) SPF 15 Daily Use Moisturizing Sunscreen (539-009), the subject of pending NDA 21-502, having as active ingredients ecamsule 2%, avobenzone 2%, and octocrylene 10%.

The objective of this study was to determine the acnegenicity and comedogenicity potential of the test product. The study was conducted in an open fashion on 44 subjects.

The principal investigator was Robert Shanahan, Ph.D., of Consumer Product Testing Co., Fairfield, NJ. The evaluations and readings were performed by (b) (4), M.D., a dermatologist.

The subjects were males and females of 18 to 40 years of age. Approximately half of the subjects were considered to be acne prone, with 10 or fewer acne lesions, while the other half had more than 10 acne lesions. Subjects were excluded from enrollment if they were currently receiving or had received systemic acne treatment within the prior six months, or had received topical acne treatment within the prior four weeks, or if they had started or changed dosage or brands of oral contraceptives within the prior six months, or if they had a menstrual cycle-dependent flare of acne lesions.

Applications of the test product were made twice daily to the face for 6 weeks. The subjects were instructed to discontinue use of their regular facial lotion/moisturizer. Other than lipstick and mascara, no cosmetic products were to be used on the face. No systemic medications were to be taken nor topical medications applied without prior consultation with the investigator. Treatment with concomitant medications was permitted if in the investigator's opinion it did not interfere with the conduct of the study or the interpretation of the results.

The number of acne lesions was counted at baseline and at return visits at weeks 4 and 6. For this evaluation the face was divided into six sites, consisting of the right and left forehead, cheeks, and chin. The number of non-inflammatory lesions (comedones) and inflammatory lesions (papules and pustules) were counted in these sites and recorded in the case report form.

A statistical analysis for acnegenicity was performed, whereby the paired

t-test was used to test the null hypothesis that the mean number of lesions at baseline for all subjects was equal to the mean number of lesions for all subjects at the final visit. An analysis for comedogenicity compared the mean comedone counts in the same manner.

Results were as follows.

44 subjects were enrolled in the study, of which 40 subjects were analyzed for acnegenicity/comedogenicity. One subject was excluded for a protocol violation, and 3 subjects did not complete the study for unrelated reasons.

The baseline characteristics of all subjects enrolled were as follows.

Baseline characteristics n=44	
Gender	
Male	24 (55%)
Female	20 (45%)
Race	
Caucasian	32 (82%)
Black	3 (7%)
Asian	2 (5%)
Hispanic	3 (7%)
Skin type	
I	2 (5%)
II	7 (16%)
III	13 (30%)
IV	12 (27%)
V	8 (18%)
VI	2 (5%)

The mean acne lesion counts and the comedone counts at baseline and return visits were as follows.

Acne lesion counts		
	Mean	Range
Baseline	7.7	1-24
Week 4	6.9	1-35
Week 6	6.6	1-36

Comedone counts		
	Mean	Range
Baseline	3.2	0-20
Week 4	2.6	0-32
Week 6	3.0	0-33

There were no statistically significant differences between the baseline and final lesion counts, nor between the baseline and final comedone counts.

The sponsor's conclusion was that, according to the results of this study, (b) (4) Sunscreen (539-009) can be considered non-acnegenic and non-comedogenic.

Reviewer's evaluation: This study was performed on a related product, (b) (4) *Sunscreen 539-009, the subject of pending NDA 21-502, having* as active *ingredients ecamsule 2%, avobenzone 2%, and octocrylene 10%. Although the mean values for acne lesions and comedones decreased from baseline, there were increased lesions of both types in one or more subjects, as indicated by the ranges of values. The individual subject data need to be examined to determine whether there is a subset of subjects in which the test product might be acnegenic/comedogenic.*

Study PEN.570.02 - Comedogenicity

The objective of this study was to assess the comedogenicity potential of two test products by determining the densities of microcomedones on follicular biopsies after repeated patch applications. This was an evaluator blind, otherwise open study, performed by Alessandra Pagnoni, M.D., of Hill Top Research, Milltown, NJ on 26 evaluable subjects.

The test products were:

- (b) (4) Sunscreen 539-106, the subject of pending NDA 21-471, containing 2% ecamsule, 2% avobenzone, 10% octocrylene, and 2% titanium dioxide.
- (b) (4) Sunscreen 760-006, the subject of the current application, containing 3% ecamsule, 2% avobenzone, and 10% octocrylene.

Acetylated lanolin alcohol served as a positive control and a blank (b) (4) patch served as a negative control.

The rationale for the study design and methodology is that comedones are

the first clinical lesions in acne, from which inflammatory lesions (papules and pustules) arise. Precursors of comedones are called microcomedones, and are visible only microscopically. Microcomedones arise due to hyperkeratosis of the sebaceous follicles. It has been demonstrated that in subjects prone to develop comedones, comedogenic substances can induce increase in microcomedones in 4 weeks when applied under occlusion to the back.

Subjects enrolled into the study were males and females, 18 to 55 years of age, who had a minimum microcomedone score of 2 on follicular biopsies taken at screening from the interscapular region of the back. Subjects excluded from enrollment were those who had participated in a clinical research study involving the test area of the back within 30 days prior to enrollment or in a comedogenicity study involving the same area of the back within 90 days prior to enrollment, those currently receiving medication that could interfere with the evaluations, such as Accutane or Ortho Tricyclen, in the prior 6 months, or other oral acne medications or topical acne medications applied to the back, or those who began or changed dosage or brands of oral contraceptives in the prior 3 months.

Four test sites, each measuring 3 cm^2, were delineated on the interscapular region of the back of each subject. The two test products and the two controls were randomly assigned to each of the test sites. Applications of 0.3 ml of the test products were made under occlusive patches three times weekly to the same test sites for four weeks. The first two weekly patches remained in place for 48 hours, while the third patch remained for 72 hours. At the end of the four week period, follicular biopsies of all test sites were performed.

Follicular biopsies were performed as follows. The test sites were first washed gently with a mild cleanser. The test area was then coated with a thin layer of methyl cyanoacrylate glue, and a plastic microscopic slide was applied to the glue and pressed firmly into place. The glue was allowed to dry for a few minutes, and the slide was then peeled off, removing a thin layer of stratum corneum with follicular horny extensions with it. The slides were examined for microcomedones using a stereomicroscope, and were scored on the following scale.

0	None to very small horny cylinders at some follicular orifices.
1	Small horny cylinders involving a few follicles.
2	Small horny cylinders involving a moderate amount of follicles, or a few larger microcomedones.
3	Small horny cylinders involving a moderate amount of follicles and a few medium or large microcomedones, or smallish horny cylinders involving most of the follicles.
4	A moderate number of medium sized microcomedones.
5	A higher number of medium sized comedones.
6	Medium sized microcomedones over most of the field or a moderate number of medium sized and large sized microcomedones.
7	Large microcomedones over most of the field.

The evaluation of comedogenicity was based on a comparison of the mean microcomedone score between the test product and the untreated control. The test material was defined as comedogenic if the mean score were significantly greater than that of the untreated control. Additional considerations for comedogenicity were the number of subjects in which the microcomedone score increased compared to the control, and the magnitude of such increase.

Results were as follows.

Thirty subjects were enrolled into the study, of which 26 subjects were evaluable. Four subjects withdrew from the study for unrelated personal reasons.

Baseline characteristics of all subjects enrolled were as follows.

Baseline characteristics n=30	
<u>Gender</u> Male Female	 7% 93%
<u>Race</u> Caucasian Black	 97% 3%

The distribution of microcomedone scores at the final visit was as follows.

Score	(b) (4) sunscreen (539-106)	(b) (4) sunscreen (760-006)	Negative control
0	3 (12%)	3 (12%)	1 (4%)
1	9 (36%)	8 (31%)	7 (27%)
2	11 (44%)	12 (46%)	13 (50%)
3	1 (4%)	2 (8%)	3 (12%)
4	1 (4%)	1 (4%)	2 (8%)

The mean scores, the differences in scores from the control, and the p values for the comparison were as follows.

	(b) (4) sunscreen (539-106)	(b) (4) sunscreen (760-006)
Mean score	1.52	1.62
Mean difference from untreated control	- 0.4	- 0.3
P value	0.0049	0.0177

Microcomedone scores at treated sites were greater than that at the untreated control site in 1 subject with formulation 539-106, 1 subject with formulation 760-006, and 15 subjects with the positive control (ALA).

Eleven adverse events that occurred at the test sites and were possibly or probably related to treatment were reported in 5 subjects. These were papular acne in 4, erythema in 2, and edema in 5. Of the cases of papular acne, 4 occurred with formulation 760-006, and 1 occurred with the positive control.

The sponsor's conclusion was that, under the conditions of the study, (b) (4) Cream (539-106) and (b) (4) Cream (760-006) were both found to be non-comedogenic. As there was a significantly greater density of microcomedones on the untreated sites, both formulations demonstrated a potential to control the formation of microcomedones.

Reviewer's evaluation: The study is interesting from a theoretical standpoint, but has no regulatory utility, as it did not utilize clinical parameters.

Reviewer's overall evaluation of Phase 1 studies: The dermal safety studies are adequate to show that there is little or no potential for irritation, phototoxicity, or photosensitization under the conditions of proposed usage. Although there were no sensitization reactions at challenge, one subject in the sensitization study was apparently pre-sensitized to the test product prior to initiation of the study. There is therefore some potential for sensitization.

The design of the comedonegenicity study 570.02 is not adequate to conclude that the test product is not acnegenic or comedogenic.

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/s/

Phyllis Huene
1/9/2006 03:33:08 PM
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Dermatology review of dermal safety. See OTC MO review for overall safety and UV sunscreen evaluation by OTC.

Stanka Kukich
3/7/2006 11:19:20 AM
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