MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 2006

FROM: Susan McCune, MD
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THROUGH: Sandra Kweder, MD
Deputy Director, OND

TO: Elaine Abraham, RPM
DNCE

SUBJECT: Combination OTC Sunscreens (Investigational Name - ____ b(4)
and Use During Pregnancy
NDAs: 21-501, 21-502, & 21-471 (L'Oreal USA Products)

Consult received by the PLT: December 8, 2005
Due date: January 31, 2006

I. EXECUTIVE SUMMARY

L'Oreal USA Products is seeking approval to market three new sunscreen products with three or four sunscreen ingredients in differing concentrations. These ingredients are avobenzone, octocrylene, titanium dioxide (all three monograph ingredients) and ecamsule (a new ingredient). Eleven women became pregnant during three studies, four infants developed birthmarks: two with hemangiomas, one with a nevus flammeus and one with a café au lait spot.

The Pregnancy & Lactation Team (PLT) was consulted to

1. 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.
2. Advise whether the OTC labeling for these new sunscreen products ____ b(4)

The PLT recommends that the sponsor be requested to provide more descriptive information on the seriousness and extent of vascular involvement for the two

cases of hemangiomas as well as the dose and duration of exposure to the drug. Given that hemangiomas develop postnatally frequently (7 – 10% of infants) and most are small and involute, the PLT does not recommend setting up a pregnancy exposure registry unless there is something unusual about the two cases, e.g., very large, life-threatening, deep, etc.

The PLT does not recommend [redacted] on the OTC labeling for these products for the following reasons:

- Ecamsule is a Pregnancy Category B drug according to the Pharm/Tox review.
- PK studies show that <1% of ecamsule is absorbed systemically
- There is no evidence of reproductive toxicity for titanium oxide, ecamsule, avobenzone or octocrylene in the literature although the data are sparse.
- There are no reports in the literature or in AERS of hemangiomas associated with the use of titanium oxide, ecamsule, avobenzone or octocrylene.

II. BACKGROUND

The following was information provided in the written consult request:

"The sponsor is requesting approval to market three new sunscreen drug products [redacted] in the over-the-counter setting (NDAs 21-501, 21-502, and 21-471). All three sunscreens contain three or four active sunscreen ingredients in different concentrations: avobenzone, octocrylene, titanium dioxide (all three monograph ingredients) and ecamsule (a new ingredient). [redacted]

Altogether, 11 women became pregnant during studies with [redacted] formulas or similar formulations. One woman (Subject #60 in Study 1.CG.03.SRE.2604) discontinued due to pregnancy and withdrew from treatment and the study. The remaining 10 women became pregnant during 2 or 4 long-term safety studies (PEN.750.02 and RD.06.SRE.18047). There were no pregnancies reported during any other studies.

Four women became pregnant in Study PEN.750.02. Two of these subjects (#12-18 and #16-35) delivered during the study. Subject 11-16 discontinued the study prior to giving birth and subject 12-36 gave birth after completing the study. All four women delivered normal healthy babies.

Six pregnancies were reported during Study RD.06.SRE.18047. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in a delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the event was assessed

by the sponsor as of no pathological significance. Three of six infants were normal at birth but subsequently developed vascular lesions approximately three months after birth. All three events of birthmarks (two hemangiomas and one nevus flammeus) were reported as serious adverse events (congenital anomaly). Family history was negative in two cases and positive in one (nevus flammeus). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. The division does not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated in pregnancy. The number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects with PLME could have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. PK studies show that <1% of ecamsule (active ingredient) is absorbed systemically."

III. REVIEW OF DATA

The following materials were reviewed:

- Medical Officer review of —— b(4)
- Pharm/Tox review of ——
- Reprotox information in the online Micromedex Intergrated Index including Teris – The Teratogen Information System, the Reprotox System and Shepard's Catalog of Teratogenic Agents
- AERs database
- Pubmed for 1. reproductive effects with avobenzone, octocrylene, titanium dioxide or ecamsule and 2. hemangiomas. The following articles were retrieved.
  - Blei F. Basic science and clinical aspects of vascular anomalies. *Current Opinion in Pediatrics* 2005;17:5011-9.
  - Chiller KG, Frieden IJ, Arbiser JL. Molecular patahogenesis of vascular anomalies: Classification into three categories based upon clinical and biochemical characteristics. Lymphatic Research and Biology 2003;1(4):267-81.
  - Chang MW. Updated classification of hemangiomas and other vascular anomalies. Lymphatic Research and Biology 2003;1(4)259-65.

The medical officer review and the pharm/tox review are from the previous submission ——). There is no information from the current submission other than what is b(4) included in the written consult. It appears that 3 studies contained women who became pregnant (N=11). One woman in study 1.CG.03.SRE.2604 became pregnant and

discontinued her participation in the trial. Four women in study PEN.750.02 became pregnant and all delivered healthy babies. Six pregnancies were reported in study RD.06.SRE.18047 which was reviewed for [redacted]. Of the 6 pregnancies, 3 infants developed "vascular lesions" approximately 3 months after birth. One was a nevus flammeus and two were reported as hemangiomas. There was no description of the hemangiomas. Dr. Eichenfield at UCSD stated that nevus flammeus is present in half of all newborns and hemangiomas occur in 10-13% of children in the first year of life. He was unaware of any reports that hemangiomas have been induced by exogenous factors such as drugs or chemicals. He felt that the hemangiomas were random findings and not related to the use of the sunscreen. b(4)

The consult mentions another patient with a cafe au lait spot but that is not discussed in the medical officer review of [redacted]. According to the consult, the cafe au lait spot was felt to be of no pathological significance "since isolated cafe au lait spots occur in up to 10-20% of the normal population". b(4)

In the Pharm/Tox review of [redacted], there was an oncogenicity study by dermal application of ecamsule to CD-1 mice for 104 weeks (p.45-51). They concluded, "The relative incidence of hemangiosarcomas compared to controls was higher in the high dose males and females. The relative incidence of hemangiomas in treated females was also increased over control. However, hemangiomas and hemangiosarcomas are not rare in the historical control data from the testing laboratory and the values from the current study appear to be within historical control ranges." b(4)

There is no evidence of reproductive toxicology for titanium dioxide, ecamsule, avobenzone or octocrylene in the literature although the data are sparse.

There are no reports in the literature of hemangiomas associated with ecamsule, avobenzone, octocrylene or titanium dioxide.

In a search of the AERS database for ecamsule, avobenzone, octocrylene, titanium oxide, and [redacted] there were a total of 61 reports. None of them mentioned hemangioma. There were no AERS reports for any children between 0-1 year of age, and there were no reports of congenital anomalies. b(4)

The literature supports the assessment that nevus flammeus occurs in approximately half of all newborns, cafe au lait spots in approximately 10 % of infants and hemangiomas in approximately 7-10% of the newborn population. Hemangiomas are more common in female infants and premature infants. They tend to grow postnatally for several months and then spontaneously involute. There are many varieties of hemangiomas in the newborn period and there was no description of the type of hemangioma in the study report. The etiology of vascular anomalies in the newborn period is unclear and likely represents a multifactorial process.

IV. CONCLUSIONS

Cutaneous vascular abnormalities occur frequently in the newborns. Unless the two cases of hemangiomas reported in the study 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.

Based on the materials reviewed the PLT does not recommend ——— be included in the OTC labeling. b(4)

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/s/

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PLT Consult for NDAs 21-471, 21-501, and 21-502

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2/8/2006 05:42:15 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-501 & 21-502 (IND 59,126)
Submission Code	N 000
Letter Date	May 16, 2005 (NDA 21-501) May 12, 2005 (NDA 21-502)
Stamp Date	
PDUFA Goal Date	March 16, 2006 (NDA 21-501) March 12, 2006 (NDA 21-502)
Reviewer Name	Daiva Shetty, MD
Review Completion Date	January 6, 2006
Established Names	Ecamsule 3%/avobenzone2%/ octocrylene 10% lotion (NDA 21-501) Ecamsule 2%/avobenzone2%/ octocrylene 10% lotion (NDA 21-502)
(Proposed) Trade Name	Several
Therapeutic Class	Sunscreen
Applicant	L'Oreal USA Products, Inc.
Priority Designation	S
Formulation	Lotions
Dosing Regimen	For NDA 21-501: Apply liberally 15 minutes before sun exposure. [redacted] For NDA 21-502: Apply evenly [redacted] before sun exposure [redacted]
Indication	Prevention of sunburn [redacted] due to sun exposure
Intended Population	Children 6 months and older and adults

b(4)

Table of Contents

1 EXECUTIVE SUMMARY 4

1.1 RECOMMENDATION ON REGULATORY ACTION 4
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS 4
1.2.1 Risk Management Activity 4
1.2.2 Required Phase 4 Commitments 4
1.2.3 Other Phase 4 Requests 4
1.3 SUMMARY OF CLINICAL FINDINGS 4
1.3.1 Brief Overview of Clinical Program 4
1.3.2 Efficacy 5
1.3.3 Safety 5
1.3.4 Dosing Regimen and Administration 6
1.3.5 Drug-Drug Interactions 6
1.3.6 Special Populations 6

2 INTRODUCTION AND BACKGROUND 7

2.1 PRODUCT INFORMATION 7
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS 8
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES 8
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS 8
2.5 PRESUBMISSION REGULATORY ACTIVITY 8
2.6 OTHER RELEVANT BACKGROUND INFORMATION 9

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 9

3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) 9
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY 9

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY 9

4.1 SOURCES OF CLINICAL DATA 9
4.2 TABLES OF CLINICAL STUDIES 10
4.3 REVIEW STRATEGY 12
4.4 DATA QUALITY AND INTEGRITY 12
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES 12
4.6 FINANCIAL DISCLOSURES 12

5 CLINICAL PHARMACOLOGY 12

5.1 PHARMACOKINETICS 13
5.2 PHARMACODYNAMICS 13
5.3 EXPOSURE-RESPONSE RELATIONSHIPS 13

6 INTEGRATED REVIEW OF EFFICACY 13

7 INTEGRATED REVIEW OF SAFETY 14

7.1 METHODS AND FINDINGS 14
7.1.1 Deaths 15
7.1.2 Other Serious Adverse Events 15
7.1.3 Dropouts and Other Significant Adverse Events 15
7.1.4 Other Search Strategies 18
7.1.5 Common Adverse Events 19
7.1.6 Less Common Adverse Events 24
7.1.7 Laboratory Findings 24
7.1.8 Vital Signs 25

7.1.9 Electrocardiograms (ECGs) 25
7.1.10 Immunogenicity 25
7.1.11 Human Carcinogenicity 25
7.1.12 Special Safety Studies 25
7.1.13 Withdrawal Phenomena and/or Abuse Potential 25
7.1.14 Human Reproduction and Pregnancy Data 26
7.1.15 Assessment of Effect on Growth 27
7.1.16 Overdose Experience 27
7.1.17 Postmarketing Experience 27
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS 31
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety 31
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 37
7.2.3 Adequacy of Overall Clinical Experience 37
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 37
7.2.5 Adequacy of Routine Clinical Testing 38
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 38
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study 38
7.2.8 Assessment of Quality and Completeness of Data 38
7.2.9 Additional Submissions, Including Safety Update 38
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS 39
7.4 GENERAL METHODOLOGY 39
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 39
7.4.2 Explorations for Predictive Factors 39
7.4.3 Causality Determination 44

8 ADDITIONAL CLINICAL ISSUES 44

8.1 DOSING REGIMEN AND ADMINISTRATION 44
8.2 DRUG-DRUG INTERACTIONS 44
8.3 SPECIAL POPULATIONS 44
8.4 PEDIATRICS 45
8.5 ADVISORY COMMITTEE MEETING 46
8.6 LITERATURE REVIEW 46
8.7 POSTMARKETING RISK MANAGEMENT PLAN 47
8.8 OTHER RELEVANT MATERIALS 47

9 OVERALL ASSESSMENT 47

9.1 CONCLUSIONS 47
9.2 RECOMMENDATION ON REGULATORY ACTION 47
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS 47
9.3.1 Risk Management Activity 47
9.3.2 Required Phase 4 Commitments 47
9.3.3 Other Phase 4 Requests 47
9.4 LABELING REVIEW 48
9.5 COMMENTS TO APPLICANT 50

10 APPENDICES 51

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS 51
10.2 LINE-BY-LINE LABELING REVIEW 53

REFERENCES 63

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed (b) (4) SPF 15 Water Resistant (W/R) lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 3%) and (b) (4) SPF 15 lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 2%) have an acceptable safety profile. They are approvable for over-the-counter (OTC) marketing from the safety stand point. Final approvability depends on the outcome of the efficacy, preclinical, and chemistry data, which are being reviewed by other reviewers.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

If these NDAs are approved, a controlled study in pregnant women should be conducted to evaluate the relationship between sunscreen exposure during pregnancy and vascular skin abnormalities in babies.

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 two new combination sunscreen drug products, (b) (4) SPF 15 water resistant lotion (NDA 21-501) and (b) (4) SPF 15 lotion (NDA 21-502), in the OTC setting for daily use in adults and children six months of age and older.

Both products contain three active ingredients in different concentrations. Two out of three (octocrylene and avobenzone) are sunscreen ingredients already marketed in the US under the Tentative Final Monograph for Sunscreen Drug Products for OTC Human Use. The third ingredient, ecamsule, is a new molecular entity in the US, even though it has been marketed in Europe, and other parts of the world since 1993.

In support of their submission, the sponsor has submitted data from a total of 28 clinical studies. Since the clinical data to support the marketing of both of the products are the same, the two NDAs are reviewed together.

1.3.2 Efficacy

The sponsor is seeking to market the two sunscreen drug products for the prevention of sunburn.

In support of product efficacy, the sponsor has submitted results of nine controlled clinical studies. These studies include the following:

- Seven sun protection factor (SPF) determination studies (including three water resistance studies)
- Two protection factor for UVA (PFA) determination studies (one by the persistent pigment darkening PPD method and one by a similar method but using the photosensitizer 8-MOP)

All of these studies are being reviewed by other reviewers in the Office of Nonprescription Products and Division of Dermatological and Dental Drug Products. Only safety findings from these studies pertinent to the two sunscreen drug products will be discussed in this review.

1.3.3 Safety

A total of 2539 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens.

There were no drug-related deaths or drug-related serious adverse events reported among the participants in clinical trials.

A total of 31 subjects in clinical studies discontinued due to adverse events (AEs). Out of those, 12 were assessed as probably, possibly or definitely related to study drug. All of these 12 AEs were related to local skin irritation and all of them resolved.

Clinical studies that contributed to the safety database were classified into three groups:

- Phase 1,2, and 3 clinical studies
- Long-term safety studies
- Supportive studies

Of the 1155 subjects in the Phase 1, 2, and 3 clinical studies, 86 subjects reported a total of 125 AEs. Seven adverse events (skin infection, pruritus and eczema) were assessed as probably or possibly related to treatment; all were mild and non-serious.

A total of 1048 subjects were exposed to one of the four ecamsule-containing sunscreen drug products during long-term safety studies (573 in (b) (4) studies and 475 in a ——— study). Drug-related adverse events reported during the three long-term (b) (4) clinical studies were

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limited to Skin and Appendages Body System and Special Senses. A total of 66 drug related AEs were reported in Skin and Appendages System and four in the Special Senses System. None of these events were assessed by the investigator as serious and all of them resolved. The profile of drug-related AEs was consistent across the 3 long-term studies, except for PEN.750.01 where a higher number of acne events were reported. This increased incidence could be partly related to a higher number of adolescents enrolled. The following AEs were the most common (incidence of ≥ 1% in individual studies) treatment-related AEs in the three long-term (b) (4) studies: acne, dermatitis, dry skin, eczema, erythema, pruritus, skin discomfort, and sunburn.

Long-term study RD.06.SRE.18047 has been reviewed in detail under the b(4)
According to the clinical reviewer, except for sunburn, adverse events which were considered to be possibly related to the study products were of low incidence and minor severity.

Seven reports of erythema/edema were considered probably related and four reports of papules possibly related in (b) (4) supportive studies. A total number of subjects in these studies were 336.

Postmarketing AEs reported to the sponsor did not reveal any serious safety issues. The most common AEs in the postmarketing database are consistent with the AE profile from the clinical trials.

1.3.4 Dosing Regimen and Administration

The proposed dosing directions for (b) (4) 15 WR lotion are:

- apply liberally 15 minutes before sun exposure
- reapply after towel drying, swimming, or perspiring b(4)
- children under 6 months of age: ask a doctor

The proposed dosing directions for (b) (4) 15 lotion are:

- apply evenly before sun exposure
- children under 6 months of age: ask a doctor

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with (b) (4) formulations. The sponsor states that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin; therefore, it is unlikely that interactions with systemic medications would occur. Subjects who participated in the clinical trials were allowed to use any systemic or topical treatments. There were no safety signals noted due to a particular drug-drug interaction.

1.3.6 Special Populations

There did not appear to be a specific association of adverse reactions with pediatric use of the sunscreens.

Based on the preclinical pharmacology data, ecamsule is a Pregnancy Category B drug. The proposed labeling does not carry any pregnancy warning. Eleven pregnant women were exposed to ecamsule-containing drug products during clinical development program, and three of them delivered babies with vascular congenital defects. In the opinion of this reviewer, the product labeling should alert pregnant or nursing women to consult a physician prior to the use of these sunscreens. The sponsor should also conduct a post-marketing controlled study in pregnant women to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in their babies.

2 INTRODUCTION AND BACKGROUND

This is a medical safety review of two sunscreen combination drug products, submitted under two different NDA numbers: 21-501 and 21-502. Since the clinical data to support the marketing of both the products are the same, the two NDAs will be reviewed together.

2.1 Product Information

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

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

For the purposes of this review, (b) (4) SPF 15 WR lotion will be also referred as SPF 15 WR or as its formulation code 760-006.

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

1. UV EXPERT
3. ANTHELIOS
5. CAPITAL SOLEIL
6.

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NDA 21-502 is for the (b) (4) SPF 15 lotion. (b) (4) SPF 15 lotion is a topical combination sunscreen composed of the following three active sunscreen ingredients:

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

For the purposes of this review, (b) (4) SPF 15 lotion will be also referred as SPF 15 or as its formulation code 539-009.

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

1. UV PROTECTIVE
2. UV ACTIVE
3. ANTHELIOS
4. [redacted]
5. UV EXPERT
6. [redacted]
7. UV DEFENDER

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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.

2.2 Currently Available Treatment for Indications

There are a total of 16 active sunscreen ingredients currently available for the prevention of sunburn to US consumers. All of them are marketed under the Tentative Final Monograph (TFM) for Sunscreen Drug Products for OTC Human Use. Two of the (b) (4) W/R lotion ingredients (avobenzone and octocrylene) are marketed in the US under the TFM as single ingredients or in combination with others.

2.3 Availability of Proposed Active Ingredient in the United States

As mentioned above, two out of three active ingredients contained in the (b) (4) 15 W/R lotion and (b) (4) 15 lotion are available in the US. The third ingredient, ecamsule, is new to the US market.

2.4 Important Issues With Pharmacologically Related Products

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

2.5 Presubmission Regulatory Activity

In addition to the two products under current review, there is a third sunscreen drug product developed under IND 59,126/NDA 21-471, (b) (4) SPF 20 Water Resistant Sunscreen (formula #539-106), also for over-the-counter use. The NDA 21-471 for the third product is being reviewed separately.

[redacted]

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

2.6 Other Relevant Background Information

Ecamsule was included in the European Economic Community (EEC) Cosmetic Directory, Annex VII, "List of UV Filters Which Cosmetic Products May Contain" in 1991 and commercialization of ecamsule-containing sunscreen products began throughout Europe and other parts of the world in 1993. Over ——— units of sunscreen products containing ecamsule have been sold worldwide. Sunscreen products are considered cosmetics in all other countries with the exception of Canada and Australia. Ecamsule was registered with the Canadian Health Protection Bureau in 1994 and the Australian Heath Authorities in 1995.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC review is pending.

3.2 Animal Pharmacology/Toxicology

The sponsor conducted a total of 87 animal and toxicology studies under the ——— cream development program. Neither ecamsule, nor ——— cream was teratogenic, carcinogenic, or photocarcinogenic. There was no embryolethality or reproductive toxicity associated with ecamsule alone or with other active sunscreen ingredients, contained in the proposed drug product. The acute oral toxicity dose in the rat was 5000 mg/kg and in the mouse, 2000 mg/kg. b(4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data to support the proposed drug products come from:

- 22 studies designed to evaluate safety and efficacy of various (b) (4) sunscreen products containing ecamsule,
- 12 studies conducted under the ——— and
- several supportive studies that contributed to safety data.

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There are three related formulations for which the sponsor is submitting NDAs for the indication of prevention of sunburn:

- (b) (4) SPF 15 W/R Lotion (NDA 21-501),
- (b) (4) SPF 15 Daily Lotion (NDA 21-502), and
- (b) (4) SPF 20 W/R Lotion (NDA 21-471).

Safety data supporting the two OTC sunscreen products reviewed in this document come from clinical studies conducted with the three formulations listed above and with [redacted] b(4). A comparison between the four related formulations is presented in Table 1 below.

Table 1. Comparative Active Sunscreen Ingredients in Different Formulations

Active Ingredients	SPF 15 WR (760-006) NDA 21-501	SPF 15 (539-009) NDA 21-502	SPF20 WR (539-106) NDA 21-471	[redacted] b(4)
Ecamsule	3.0%	2.0%	2.0%	3.0%
Avobenzone	2.0%	2.0%	2.0%	
Octocrylene	10.0%	10.0%	10.0%	
Titanium Dioxide	NA	NA	2.0%	

4.2 Tables of Clinical Studies

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Table 2. List of Clinical Studies to Support the NDA

	Study #	Product	Type of Study
	PK		
1	V99.1203	2% ecamsule	PK in healthy volunteers
2	V3156	4.95% ecamsule	PK in healthy volunteers
3	1.CG.03SRE.2607	[redacted]	Absorption study
	Efficacy		
4	PEN.820.01	SPF15WR,SPF20WR	SPF
5	PEN.820.02	SPF15WR,SPF20WR	SPF
6	9901.001.COS	SPF15WR	Screening
7	PEN.910.01	All three*	PFA
8	PEN.920.01	All three	PFA
9	PEN.810.01	SPF 15	SPF
10	PEN.810.02	SPF 15	SPF
	Supportive		
11	PEN.810.03	SPF20WR	SPF
12	PEN.810.04	SPF20WR	SPF
13	PEN.810.05	Many different	SPF for individual ingredients
14	PEN.810.06	Many different	SPF for individual ingredients
15	PEN.910.02	Many different	PFA for individual ingredients
	Support of Combination		
16	1.CG.03.SRE.2612	[redacted]	SPF
17	1.GUS.05.SRE.18045.R01	[redacted] +triads	SPF
18	1.GUS.05.SRE.2639	[redacted] triads	SPF
19	1.CG.03.SRE.2613	[redacted] triads	UVA
20	1.CG.03.SRE.2614	[redacted] +triads	UVA
	Efficacy [redacted]		
21	RD.06.SRE.18057	[redacted] +triads	Efficacy/safety
22	RR.06.SRE.2616	[redacted] +triads	Efficacy/safety
	In-vitro studies		
23	S01-0205	All three	Critical wavelength (Diffey)
24	SOL-DP-97-021	[redacted]	Combo
25	D20041030	Many different	Combo
	Safety Studies		
26	PEN.110.01	All three	Repeat patch test
27	PEN.210.01	All three	Photoallergy potential
28	PEN.250.01	All three	Phototoxicity
29	1.CG.03.SRE.2604	[redacted] +triads	Contact sensitization/irritancy
30	1.CG.03.SRE.2605.R01	[redacted] +triads	Phototoxicity
31	1.CG.03.SRE.2606	[redacted] +triads	Photoallergy
32	PEN.750.02	SPF 15 WR	Long-term safety
33	PEN.750.01	SPF15	Long-term safety
34	PEN.750.03	SPF20 WR	Long-term safety
35	RD.06.SRE.18047	[redacted]	Long-term safety [redacted]
	Other Studies		
36	PEN.570.01	SPF15	Acnegenicity/camedogenicity
37	PEN.570.02	SPF15WR/SPF20WR	Camedogenicity
38	PEN.1010.01	All three	Moisturization

* all three = SPF15 + SPF15WR + SPF20WR

b(4)

4.3 Review Strategy

This review covers safety data submitted to support the NDAs 21-501 and 21-502. Efficacy data, dermal tolerance studies, and studies to support cosmetic claims for the products will be reviewed by the reviewers in the Division of Dermatologic and Dental Drug Products (DDDDP) and the interdisciplinary scientist in the Office of Nonprescription Products (ONP).

4.4 Data Quality and Integrity

Even though ecamsule is a new molecular entity, it has been marketed for more than a decade in Europe and other countries. During the review, there were no discrepancies noted either in data or its analyses. Therefore, there were no DSI audits conducted for the study sites or data analyses.

4.5 Compliance with Good Clinical Practices

All clinical studies were conducted under the sponsorship of the applicant and its affiliates and were reviewed and approved by Independent Ethics Committees and Institutional Review Boards. Informed consent from participants was obtained in accordance with 21 CFR parts 50 and 56 and/or 312.120. The full clinical program was performed in compliance with Good Clinical Practice (GCP) including archiving of essential study documents.

The sponsor states that 15 cosmetic studies were not run according to GCP standards with a study product not manufactured according to Good Manufacturing Practices. These studies were performed in Europe on cosmetic sunscreens and were not included in the Integrated Summary of Safety Analysis.

4.6 Financial Disclosures

The sponsor submitted Form 3454 certifying that the investigators of all but three clinical studies did not have any significant financial interests in these products, conducted studies, or the company conducting the studies. Three of the studies for which certification was not provided, were previously reviewed under ⟶ None of these studies are pivotal for the evaluation of efficacy or safety of the two sunscreen products submitted under NDA 21-501 and 21-502.

b(4)

5 CLINICAL PHARMACOLOGY

The sponsor submitted a total of six clinical studies and seven pharmacokinetic studies (four in vitro studies and three in vivo studies) to assess pharmacology of the two sunscreen drug products. The clinical studies include the following:

- three dermal tolerance studies (one contact sensitization, PEN.110.01, one photoallergy, PEN.210.01, one phototoxicity, PEN.250.01)

- three Phase 2 OTC Sunscreen Monograph Drug Combination Policy Rule studies (two SPF, PEN.810.05 & PEN.810.06, and one PFA, PEN.910.02)

All of the studies submitted under this section are being reviewed by other reviewers in DDDDP and ONP. Clinical safety findings from these studies pertinent to the two sunscreen drug products being reviewed are discussed in Section 7 of this review.

5.1 Pharmacokinetics

Three in vivo (1.CG.03.SRE.2607, V99.1203, and V3156) and four in vitro (RDS.03.SRE.4689, 16039/G2347, 23 July 1990 Mexoryl SX study, and 26 July 1990 Mexoryl SX study) pharmacokinetic studies showed low percutaneous absorption of ecamsule using different methodologies and analysis methods. For detailed review of the studies refer to the discipline-specific reviews.

5.2 Pharmacodynamics

There are no pharmacodynamic data submitted to these NDAs.

5.3 Exposure-Response Relationships

There are no data on exposure-response relationships submitted to these NDAs.

6 INTEGRATED REVIEW OF EFFICACY

The sponsor is seeking to market the two sunscreen drug products for the prevention of sunburn.

In support of product efficacy, the sponsor submitted results of nine controlled clinical studies. These studies include the following:

- Seven sun protection factor (SPF) determination studies (including three water resistance studies)
- Two protection factor for UVA (PFA) determination studies (one by the persistent pigment darkening PPD method and one by a similar method but using the photosensitizer 8-MOP)

All of these studies are being reviewed by other reviewers in ONP and DDDDP. Only safety findings from these studies pertinent to the two sunscreen drug products will be discussed in the next section of this review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data to support the two NDAs comes from different sources:

- Phase 1, 2, and 3 clinical studies
- Phase 3 long-term safety studies
- Post-marketing safety data
- Review of the literature

For the purposes of this review, clinical studies to support safety are classified into three groups:

1. Phase 1, 2, and 3 clinical studies:
   - PEN.110.01
   - PEN.210.01
   - PEN.250.01
   - 1.CG.03.SRE.2604
   - 1.CG.03.SRE.2605.R01
   - 1.CG.03.SRE.2606
   - 1.CG.03.SRE.2607
   - V99.1203
   - V3156
   - PEN.810.05
   - PEN.810.06
   - PEN.910.02
   - PEN.810.01
   - PEN.810.02
   - PEN.820.01
   - PEN.820.02
   - PEN.910.01
   - PEN.920.01
   - PEN.99001.01.COS
2. Phase 3 long-term safety studies:
   - PEN.750.01
   - PEN.750.02
   - PEN.750.03
   - RD.06.SRE.18047
3. Other supportive studies:
   - PEN.570.01
   - PEN.570.02
   - PEN.1010.01
   - RD.06.SRE.2616
   - RD.06.SRE.18057

The first group of studies will be reviewed in detail by other reviewers. The safety data gathered during those studies are included in this review. The second group of studies includes three long-term (b) (4) safety studies (PEN.750.01, PEN.750.02, and PEN.750.03) and one safety study (RD.06.SRE.18047). Safety results gathered during these four studies will be reviewed together. Details of the three (b) (4) long-term studies are discussed in the Appendices 10.1.1 through 10.1.3 of this review. For detailed review of the long-term safety study RD.06.SRE.1807, see

b(4)

7.1.1 Deaths

There were no deaths in the Phase 1, 2, and 3 clinical studies or the supportive (b) (4) or SX cream studies.

In the four long-term safety studies, there was one death (intentional injury) reported in Study PEN.750.01, which was unrelated to study medication.

7.1.2 Other Serious Adverse Events (SAE)

There were no serious adverse events in the Phase 1, 2, and 3 clinical studies or supportive studies.

There were 32 subjects with serious adverse events among the four long-term safety studies. All SAEs were considered unrelated to study medication.

There was one SAE in the ——— ream study, RD.06.SRE.18057. Subject 143, a 50-year-old Caucasian woman, was diagnosed with thyroid cancer. The event occurred prior to the start of treatment and was assessed as unrelated to study drug. b(4)

7.1.3 Dropouts and Other Significant Adverse Events

Phase 1, 2, and 3 Clinical Studies

Completion rates were high in the Phase 1, 2, and 3 clinical studies. Overall, 1155 subjects were enrolled and 1094 (94.7%) completed the studies. Sixty-two (5.5%) subjects discontinued. The most frequent reason for discontinuation in these studies was protocol violation (18 subjects, 1.8%), followed by subject request (16 subjects, 1.4%).

Summary of subject disposition in Phase 1, 2, and 3 clinical studies is listed in Table 3 below.

Table 3. Summary of Subject Disposition in Phase 1, 2, & 3 Clinical Studies

			Discontinuation Reason					
Study #	Enroll	Complete	AE	Protocol violation	Non-medical	Lost to f/u	Subject request	Other
Phase 1 Local Tolerance Studies								
PEN.110.01	223	217	0	0	5	1	0	0
PEN.210.01	137	107	1	18	0	0	11	0
PEN.250.01	26	26	0	0	0	0	0	0
1.GC.03.SRE.2604	225	210	7	0	0	0	2	6
1.CG.03.SRE.2605.R01	30	30	0	0	0	0	0	0
1.CG.03.SRE.2606	118	112	4	0	0	0	2	0
Phase 1 Pharmacokinetic Studies								
1.CG.03.SRE.2607	6	6	0	0	0	0	0	0
V99.1203	5	5	0	0	0	0	0	0
V3156	8	7	1	0	0	0	0	0
Phase 2 Combination Policy Studies								
PEN.810.05	50	49	0	0	0	0	0	1*
PEN.810.06	100	99	0	0	0	0	1	0
PEN.910.02	70	70	0	0	0	0	0	0
Phase 3 UVA/UVB Protection Studies								
PEN.810.01	21	21	0	0	0	0	0	1
PEN.810.02	20	20	0	0	0	0	0	0
PEN.820.01	21	21	0	0	0	0	0	0
PEN.820.02	25	24	0	0	0	0	0	1**
PEN.910.01	32	32	0	0	0	0	0	0
PEN.920.01	14	14	0	0	0	0	0	0
PEN.99001.01COS	24	24	0	0	0	0	0	0
Total	**1155**	**1094**	**13**	**18**	**5**	**1**	**16**	**9**

* Used exclusionary medication; ** Failure to complete Day 2 visit

Discontinuation due to adverse events in these studies was 1.1% (13 subjects). One subject in the Phase 1 local tolerance studies (Study PEN.210.01) withdrew due to an AE. Subject 116 was discontinued from the study PEN.210.01 due to a severe sinus infection that began on November 11, 2000 and required exclusionary concomitant medication. The sinus infection resolved on November 13, 2000.

One subject in PK study V3156 withdrew from the study due to a joint disorder that was considered mild and unrelated to treatment.

In the —— Cream study 1.CG.03.SRE.2606, there were four subjects who discontinued due to adverse events (one with mild cold, one with mild asthenia, one with severe pharyngitis, and one with moderate tendonitis). The investigator considered all adverse events non-serious and unrelated to study treatment. All adverse events resolved.

Seven of 225 subjects in Study 1.CG.03.SRE.2604 discontinued due to adverse events. Six events were assessed as unrelated to study treatment. One mild general pruritus event was assessed as possibly related to study treatment.

Phase 3 Long-Term Studies

Subject disposition in four long-term safety studies is summarized in Table 4.

Table 4. Subject Disposition in Long-Term Safety Studies

	Number (%) of Subjects			
	PEN.750.01 Daily Use	PEN.750.02	PEN.750.03	RD.06.SRE.18047
		Intermittent Use		
Status	**(N=248)**	**(N=246)**	**(N=80)**	**(N=475)**
Subjects enrolled	248 (100%)	246 (100%)	80 (100%)	475 (100%)
Subjects completed	205 (82.66%)	180 (73.17%)	67 (83.80%)	278 (58.5%)
Subjects discontinued	43 (17.34%)	66 (26.83%)	13 (16.25%)	197 (41.5%)
Adverse events	4 (9.30%)	3 (4.55%)	0 (0.00%)	12 (2.5%)
Subject request	16 (37.21%)	24 (36.36%)	3 (23.08%)	117 (24.6%)
Protocol violation	4 (9.30%)	1 (1.52%)	0 (0.00%)	4 (0.8%)
Lost to follow-up	18 (41.86%)	18 (27.27%)	9 (69.23%)	40 (8.4%)
Other	1 (2.33%)	20 (30.30%)	1 (7.69%)	21 (4.4%)
Subjects in Safety Population	248 (100%)	246 (100%)	79 (98.75%)	475 (100%)

b(4)

Completion rates in (b) (4) long-term studies ranged from 73% to 84% of subjects. Discontinuation rates ranged from 16% to 27%. The most frequent reasons for discontinuation were subject request and lost to follow-up. The incidence of discontinuation due to adverse events in the (b) (4) studies was less than 10% in each study. Higher overall discontinuation rate (42%) was seen in study RD.06.SRE.18047, however, discontinuation due to adverse events was low (2.5%) during this study.

There were 19 (6%) discontinuations due to AEs across the three studies, four in PEN.750.01, three in PEN.750.02, and 12 in RD.06.SRE.18047. Table 5 summarizes these subjects.

Table 5. Summary of Subjects Who Discontinued due to AEs in Long-Term Studies

Study #	Subject #	Age/ Gender	Event	Relationship	Outcome
PEN.750.01	6-12	13/F	Intentional injury	Unrelated	Death
	8-33	58/F	Arthritis	Unlikely	Ongoing
	10-12	60/F	Erythema and hives (3 days)	Probably	Resolved
	10-34	58/F	Facial itching (1 day)	Probably	Resolved
PEN.750.02	12-10	4/M	Rash (3 days)	Definitely	Resolved
	16-04	8/M	Rash (2 days)	Definitely	Resolved
	16-05	5/M	Rash (2 days)	Definitely	Resolved
RD.06.SRE.18047	157	13/F	Photosensitivity	Possibly	Resolved
	251	43/F	Abnormal liver function tests	Unlikely	Ongoing
	314	38/F	Acne	Possibly	Resolved
	367	52/F	Increased serum creatinine	Unlikely	Resolved
	490	79/F	Pruritus	Possibly	Resolved
	497	61/F	Skin discomfort	Probably	Resolved
	515	49/F	Photosensitivity	Unlikely	Resolved
	573	58/F	Pruritus	Probably	Ongoing
	757	34/F	Miliaria	Possibly	Resolved
	759	62/F	Colon Cancer	Unlikely	Resolved
	784	59/F	Nosocomial infection	Unlikely	Resolved
	806	12/F	Urticaria	Unlikely	Resolved

Other Supportive Studies

Completion rates were high in both types of supportive studies, (b) (4) and ——— cream (Table 6). (4)

Table 6. Summary of Subject Disposition in Other Supportive Studies

Study #	Enroll	Complete	Discontinuation Reason					
			AE	Protocol Violation	Non-Medical	Lost-to-f/u	Subject Request	Other
(b) (4) **Cosmetic Support Studies**								
PEN.570.01	44	40	0	0	0	0	0	4
PEN.570.02	30	26	0	0	0	0	4	0
PEN.1010.01	32	32	0	0	0	0	0	0
Other Formulations Containing Ecamsule (——— Cream Studies)								
RD.06.SRE.18057	144	140	4	0	0	0	0	0
RD.06.SRE.2616	86	79	6	1	0	0	0	1
Total	**336**	**317**	**10**	**1**	**0**	**0**	**4**	**5**

No subjects in the supportive (b) (4) studies (PEN.570.01, PEN.570.02 or PEN.1010.01) discontinued due to adverse events.

Ten subjects discontinued due to adverse events in the two ——— Cream supportive studies in subjects ——— (RD.06.SRE.2616 and RD.06.SRE.18057). The events were as follows: sunburn, accidental injury, arthritis, dyspnea, and chest pain. All adverse events were assessed as unlikely related to study treatment. (4)

7.1.3.1 Overall profile of dropouts

The majority of discontinuations were not related to adverse events.

7.1.3.2 Adverse events associated with dropouts

A total of 31 subjects in clinical studies discontinued due to adverse events. Out of those, 12 were assessed as probably, possibly or definitely related to study drug. All of these 12 AEs were related to local skin irritation, and all resolved.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, common drug-related events associated with sunscreen use include the following reactions:[1]

- Rash
- No drug effect
- Application site reaction
- Pruritus
- Paresthesia
- Skin discoloration
- Allergic reaction
- Facial edema
- Pain
- Photosensitivity
- Urticaria
- Contact dermatitis
- Hyperesthesia

7.1.5.1 Eliciting adverse events data in the development program

During clinical studies, at each follow-up visit, the investigator:

- examined all areas of skin where the subject applied study drug, specifically looking for cutaneous signs of irritation, sensitization, or photosensitivity
- asked the subject an open question regarding their health and medical status since the last visit
- reviewed the subject's diary for any information indicating a change in status from baseline or any adverse events.

Subject were encouraged to come to the study site any time they experienced a severe adverse drug event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AE reports observed during clinical studies were grouped by preferred terms using the COSTART dictionary.

7.1.5.3 Incidence of common adverse events

The incidences of adverse events in clinical studies were relatively low. The most common AEs were related to local reactions at the site of application of the study product.

[1] Sunscreen drug products for over-the-counter human use; Amendment to the tentative final monograph. Food and Drug Administration. Federal Register 61(180):48645-48655, September 16, 1996

7.1.5.4 Common adverse event tables

Tables 7 through 11 display AEs reported during clinical studies.

Table 7. Summary of AEs in Phase 1, 2, and 3 Clinical Studies

Study #	N	No. of AEs	Subjects with AEs	Types of AEs (cases)
Phase 1 Local Tolerance Studies				
PEN.110.01	223	18	14	Headache, head cold, teeth extraction, cough, fatigue, upset stomach, fever, back spasm, acid reflux, right knee surgery, toothache, pain in mouth, neck sprain, back sprain
PEN.210.01	137	5	4	Headache, sinus infection, backache
PEN.250.01	26	0	0	--
1.GC.03.SRE.2604	225	66	53	Flu syndrome, pharyngitis, cold (coryza), headache, sore throat, tooth disorders, GI events, general pruritus, itchiness around eyes, 3 reactions
1.CG.03.SRE.2605.R01	30	0	0	to — tape*
1.CG.03.SRE.2606	118	4	4	--
				Pharyngitis, asthenia, cold, tendonitis
Phase 1 Pharmacokinetic Studies				
1.CG.03.SRE.2607	6	18	6	Dizziness, headache, pruritus, eczema, infected skin
V99.1203	5	6	3	Toothache, myalgia, right shoulder pain, abdominal cramps, nausea
V3156	8	1	1	Joint disorder
Phase 2 Combination Policy Studies				
PEN.810.05	50	1	1	Sore throat
PEN.810.06	100	1	1	Headache
PEN.910.02	70	0	0	--
Phase 3 UVA/UVB Protection Studies				
PEN.810.01	21	0	0	--
PEN.810.02	20	0	0	--
PEN.820.01	21	0	0	--
PEN.820.02	25	0	0	--
PEN.910.01	32	0	0	--
PEN.920.01	14	3	3	Headache, sore throat
PEN.99001.01COS	24	0	0	--
Total	**1155**	**125**	**86**	

b(4)

b(4)

* — tape is a part of an adhesive patch used for the application of test drugs in sensitization studies

Table 8. Study PEN.750.01: Summary of AEs that Occurred in >1% of Subjects (N=248)

Body System	Preferred Term	All AEs N (%)	TRAEs* N (%)
Total		**145 (58.5)**	**39 (15.7)**
Body as Whole	Accidental injury	16 (6.5)	0
	Allergic Reaction	10 (4.0)	0
	Back pain	4 (1.6)	0
	Fever	6 (2.4)	0
	Flu symptoms	40 (16.1)	0
	Headache	31 (12.5)	0
	Infection	11 (4.4)	0
	Pain	6 (2.4)	0
	Surgical/medical procedure	5 (2.0)	0
Cardiovascular System	Hypertension	3 (1.2)	0
Digestive System	Dyspepsia	4 (1.6)	0
	Gastrointestinal disorder	3 (1.2)	0
	Nausea	3 (1.2)	0
	Tooth disorder	6 (2.4)	0
Musculo-Skeletal System	Bone disorder	3 (1.2)	0
Nervous System	Depression	3 (1.2)	0
	Dizziness	5 (2.0)	0
	Neuralgia	4 (1.6)	0
Respiratory system	Asthma	4 (1.6)	0
	Bronchitis	5 (2.0)	0
	Cough increased	3 (1.2)	0
	Pharyngitis	7 (2.8)	0
	Rhinitis	10 (4.0)	0
	Sinusitis	8 (3.2)	0
Skin and Appendages	Acne	17 (6.9)	12 (4.8)
	Contact dermatitis	3 (1.2)	0
	Dermatitis	14 (5.6)	7 (2.8)
	Dry skin	8 (3.2)	3 (1.2)
	Eczema	3 (1.2)	3 (1.2)
	Erythema	10 (4.0)	3 (1.2)
	Excoriation	3 (1.2)	0
	Pruritus	7 (2.8)	5 (2.0)
	Rosacea	3 (1.2)	1 (0.4)
	Seborrhea	4 (1.6)	2 (0.8)
	Skin burn	4 (1.6)	0
	Skin discomfort	4 (1.6)	3 (1.2)
	Sunburn	10 (4.0)	2 (0.8)
Special Senses	Conjunctivitis	6 (2.4)	2 (0.8)
	Taste perversion	3 (1.2)	1 (0.4)
Urogenital System	Urinary tract infection	5 (2.0)	0

* TRAE: treatment related adverse event

Table 9. Study PEN.750.02: Summary of AEs that Occurred in >1% of Subjects (N=246)

Body System	Preferred Term	All AEs N (%)	TRAEs* N (%)
Total		**167 (67.9)**	**18 (7.3)**
Body as Whole	Abdominal pain	5 (2.0)	0
	Accidental injury	33 (13.4)	0
	Allergic Reaction	10 (4.1)	0
	Fever	29 (11.8)	0
	Flu symptoms	52 (21.1)	0
	Headache	17 (6.9)	0
	Infection	23 (9.3)	0
	Pain	16 (6.5)	0
	Surgical/medical procedure	3 (1.2)	0
Digestive System	Gastritis	8 (3.3)	0
	Vomiting	9 (3.7)	0
Hemic/Lymphatic System	Ecchymosis	5 (2.0)	0
Musculo-Skeletal System	Myalgia	4 (1.6)	0
Respiratory system	Asthma	4 (1.6)	0
	Bronchitis	4 (1.6)	0
	Cough increased	21 (8.5)	0
	Lung disorder	5 (2.0)	0
	Pharyngitis	7 (2.8)	0
	Rhinitis	29 (11.8)	0
	Sinusitis	12 (4.9)	0
Skin and Appendages	Bite	9 (3.7)	0
	Contact dermatitis	3 (1.2)	0
	Dermatitis	20 (8.1)	7 (2.8)
	Eczema	6 (2.4)	1 (0.4)
	Erythema	8 (3.3)	2 (0.8)
	Miliaria	3 (1.2)	0
	Skin discomfort	3 (1.2)	2 (0.8)
	Skin infection	3 (1.2)	0
	Sunburn	13 (5.3)	4 (1.6)
Special Senses	Conjunctivitis	6 (2.4)	1 (0.4)
	Ear pain	6 (2.4)	0
	Otitis media	25 (10.2)	0

* TRAE: treatment related adverse events

Table 10. Study PEN.750.03: Summary of AEs that Occurred in >1% of Subjects (N=79)

Body System	Preferred Term	All AEs N (%)	TRAEs N (%)
Total		**55 (69.6)**	**3 (3.8)**
Body as Whole	Accidental injury	18 (22.8)	0
	Allergic Reaction	3 (3.8)	0
	Fever	13 (16.5)	0
	Flu symptoms	32 (40.5)	0
	Headache	4 (5.1)	0
	Infection	5 (6.3)	0
	Neck rigidity	1 (1.3)	0
	Pain	5 (6.3)	0
Digestive System	Constipation	1 (1.3)	0
	Diarrhea	3 (3.8)	0
	Gastritis	2 (2.5)	0
	Gastroenteritis	1 (1.3)	0
	Ulcerative colitis	1 (1.3)	0
	Vomiting	3 (3.8)	0
Hemic/Lymphatic System	Lymphangitis	1 (1.3)	0
Metabolic Nutritional	Dehydration	1 (1.3)	0
Nervous System	Anxiety	1 (1.3)	0
Respiratory system	Asthma	2 (2.5)	0
	Bronchitis	2 (2.5)	0
	Cough increased	11 (13.9)	0
	Lung disorder	1 (1.3)	0
	Pharyngitis	2 (2.5)	0
	Rhinitis	9 (11.4)	0
	Sinusitis	4 (5.1)	0
Skin and Appendages	Acne	3 (3.8)	0
	Bite	5 (6.3)	0
	Dermatitis	11 (13.9)	2 (2.5)
	Desquamation	1 (1.3)	0
	Dry skin	1 (1.3)	0
	Eczema	2 (2.5)	1 (1.3)
	Erythema	5 (6.3)	0
	Melanosis	3 (3.8)	0
	Skin edema	1 (1.3)	0
	Skin hypertrophy	1 (1.3)	0
	Skin infection	2 (2.5)	0
	Skin neoplasm	9 (11.4)	0
	Sunburn	2 (2.5)	0
Special Senses	Conjunctivitis	2 (2.5)	0
	Ear pain	1 (1.3)	0
	Otitis media	8 (10.1)	0
Urogenital System	Kidney calculus	1 (1.3)	0
	Kidney pain	1 (1.3)	0

Table 11. Summary of AEs in (b) (4) Supportive Studies

Study No.	N	AEs	Subjects with AEs	Types of AEs (cases)
PEN.570.01	44	0	0	--
PEN.570.02	30	13	7	Erythema/edema, erythema, papules, ankle sprain, head cold
PEN.1010.01	32	0	0	--
Total	**106**	**13**	**7**	

7.1.5.5 Identifying common and drug-related adverse events

A total of seven adverse events (skin infection, pruritus and eczema) probably or possibly related to treatment were reported in Phase 1, 2, and 3 clinical trials (see Table 7, section 7.1.5.4). All events were assessed as mild and non-serious.

Drug-related adverse events reported during the three long-term (b) (4) clinical safety studies were limited to Skin and Appendages Body System and Special Senses. A total of 66 drug related AEs were reported in Skin and Appendages System and four in the Special Senses System. None of these events were assessed by the investigator as serious and all of them resolved. The profile of drug-related AEs was consistent across the 3 long-term safety studies except for PEN.750.01 where a higher incidence of acne was reported. This increased incidence may be related to a higher number of adolescents enrolled.

Long-term study RD.06.SRE.18047 was reviewed in detail under ——— The reviewer stated that adverse events possibly related to the study products were of low incidence and minor severity, with the exception of sunburn.

Seven reports of erythema/edema were considered probably related and four reports of papules possibly related to the use of study drug in (b) (4) supportive studies. b(4)

7.1.5.6 Additional analyses and explorations

There were no additional analyses or extrapolations performed by the sponsor.

7.1.6 Less Common Adverse Events

The number of adverse events in the clinical studies were too small to assess the incidence of less common AEs.

7.1.7 Laboratory Findings

Except for urine pregnancy testing, there were no routine laboratory tests performed in the clinical safety studies for the potential OTC sunscreen products, subject of the two NDAs.

Laboratory evaluations were performed in Study 1.CG.03.SRE.2607 with ——— Cream, which evaluated percutaneous absorption of ecamsule when tested under maximized conditions. b(4)

Laboratory evaluations included hematology, serum chemistries, and urinalysis, at baseline and the end of the study. No laboratory abnormalities appeared during the study.

In study RD.06.SRE.18047 (the Phase 3, open-label study) in subjects with —— routine laboratory tests (hematology, serum chemistry and urinalysis) were performed at screening, Month 6 and Month 12 or at study discontinuation. b(4)

Overall, 58 (12.2%) patients had 77 laboratory AEs. The most prevalent abnormalities were hyperlipdemia including hypertryglyceridemia (12 patients, 2.5%) and hypercholesterolemia (9 patients, 1.9%). No fasting conditions were required by the protocol, explaining some of the variation observed during the study. Two patients (# 251 and 367) discontinued due to an increase in liver function tests (which were present at screening) and elevated creatinine. There were no clinically significant changes in the incidences of pathological laboratory parameters from screening to final visit. For detailed review of these studies see b(4)

7.1.8 Vital Signs

There were no vital sign monitoring in the (b) (4) clinical safety studies.

7.1.9 Electrocardiograms (ECGs)

There were no ECGs performed during any of the clinical studies.

7.1.10 Immunogenicity

Immunogenicity of the tested sunscreen formulations was not assessed.

7.1.11 Human Carcinogenicity

There were no data on human carcinogenicity submitted to this application.

7.1.12 Special Safety Studies

Special safety studies have been conducted to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity. These studies are being reviewed by reviewers in the Division of Dermatologic and Dental Drug Products, and will not be discussed in this review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no reason to believe that sunscreen drug products have the potential to be abused.

7.1.14 Human Reproduction and Pregnancy Data

Altogether, 11 women became pregnant during studies with (b) (4) formulas or similar formulations. One woman (Subject #60) in Study 1.CG.03.SRE.2604 discontinued due to pregnancy and withdrew from treatment and the study. The remaining 10 women became pregnant during 2 of 4 long-term safety studies (PEN.750.02 and RD.06.SRE.18047). There were no pregnancies reported during any other studies.

Four women became pregnant in Study PEN.750.02. Two of these subjects (#12-18 and #16-35) delivered during the study. Subject 11-16 discontinued the study prior to giving birth and Subject 12-36 gave birth after completing the study. Only one of four women (Subject 12-36) discontinued from the study after learning of her pregnancy. All four women delivered normal healthy babies.

Six pregnancies were reported during Study RD.06.SRE.18047. Of the six women who reported pregnancy, three discontinued because of their pregnancy. Two of the six pregnancies resulted in delivery of normal healthy babies. One infant developed a café au lait spot 1 to 2 weeks after birth. Since isolated café au lait spots occur in up to 10-20% of the normal population, the sponsor considered the event of no pathological significance. Three of six infants were normal at birth but subsequently developed vascular lesions approximately three months after birth. All three lesions (two hemangiomas and one nevus flammeus) were reported as serious adverse events (congenital anomaly). Family history was negative in two cases and positive in one (nevus flammeus). For the two cases of hemangioma, the events were considered possibly related to study treatment; the case of nevus flammeus was considered of unlikely relationship to study treatment.

According to the pharmacology review, ecamsule is a Pregnancy Category B drug. Following are the conclusions from the pharmacology review:

"Embryofetal toxicity studies have been conducted in rats with oral doses of ecamsule of up to 300 mg/kg (2 times the maximum human dose based on a body surface area comparison) and with topical application in rabbits with doses of up to 600 mg/kg (8 times the maximum human dose based on a body surface area comparison) and have revealed no evidence of harm to the fetus.

A pre- and postnatal developmental study has been conducted in rats with oral doses of ecamsule of up to 1000 mg/kg (6.5 times the maximum human dose based on a body surface area comparison) and has revealed no effects on the reproductive parameters in F0 females and no effects on the physical or behavioral development of the F1 generation. The F1 generation also had normal reproductive function after reaching sexual maturity.

There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Ecamsule did not reveal any potential to impair fertility or to induce embryo-fetal abnormalities. Development of off-spring was not affected by treatment with high doses of ecamsule."

Comments:
Based on the preclinical data, ecamsule is not a teratogen and does not have an effect on reproductive function in animals. We do not have data for the other two monograph active ingredients (avobenzone and octocrylene), which are not contraindicated during pregnancy. In addition, percutaneous absorption study (1.CG.03SRE.2607) did not reveal percutaneous penetration of ecamsule in most subjects when tested under maximized conditions. However, the number of women exposed to the sunscreen formulations containing ecamsule is small. Three congenital vascular adverse events occurred in subjects — :ould have occurred by chance alone. Nevertheless, the exposure to drug product could be significant if used as directed. Therefore, in the opinion of this reviewer, the product labeling should carry a pregnancy warning as specified in the 21 CFR 201.63 (a): "If pregnant or breast-feeding, ask a healthcare professional before use." The sponsor should also conduct a Phase 4 controlled study in pregnant women to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in their babies.

7.1.15 Assessment of Effect on Growth

There were no assessments of effects on growth in this application.

7.1.16 Overdose Experience

Given the intended route of administration (topical) and the low level of percutaneous absorption, overdosage is unlikely. No reports of overdosage have been reported in any of the clinical studies.

7.1.17 Postmarketing Experience

Postmarketing safety data for ecamsule-containing products comes from two sources:

- L'Oreal Cosmetovigilance, and
- Literature

The sponsor's postmarketing safety database will be reviewed in this section. The literature review is discussed in the Section 8.6 of this review.

L'Oreal Postmarketing Pharmacovigilance/Cosmetovigilance Data Review

The original NDA 21-501 and NDA 21-502 submissions covered cosmetovigilance safety information from 1993 through 2002. On September 13, 2005 the sponsor submitted the 120 day safety update, where safety data from the same postmarketing system was updated for the additional one year, between 2002 and the end of 2003. The sponsor did not analyze this updated information separately; rather it was discussed in a context of all 11 years together.

Therefore, all the postmarketing information (original and updated) will be discussed together in this section of the review.

There are two working databases, one is the Galderma (an affiliate of L'Oreal) phramacovigilance system and the second is the L'Oreal cosmetovigilance system. As marketing has been discontinued by Galderma in 2001 and no reports of adverse events have been received by Galderma in at least the past three years, the Galderma database did not have an update.

The L'Oreal cosmetovigilance system is designed to identify adverse reactions that may be related to cosmetic products. In preparation of this report, the sponsor reviewed all ecamsule-containing products. These products may contain ecamsule in combination with other US approved OTC sunscreen filters, but also may contain ecamsule in combination with filters not approved in the US but listed in the EEC Cosmetic Directive Annex VII. COSTART preferred terms were used for classification of all AEs reported to L'Oreal postmarketing system.

From 1993 through 2003, more than ——— of active dry ecamsule or — metric tons of the 33% solution have been produced by the L'Oreal subsidiary, CHIMEX, S.A. for commercial use. Approximately ——— units of ecamsule containing products (including beach sunscreen products, daily-use moisturizers with sunscreens and makeup products) have been sold in 15 countries where the cosmetovigilance system is in place. b(4)

For all reported spontaneous adverse reactions, a conservative estimate of 55 adverse events per million units sold of all ecamsule-containing product formulations has been reported during 11 years of marketing through 2003, an overall adverse event incidence of 0.0055% (derived from a total of — spontaneous adverse events reported during the same time period and ——— units sold). The incidence of adverse reports is relatively stable over time. A summary of incidence of AEs by year reported in the cosmetovigilance system for ecamsule containing products is presented in Table 12 below. b(4)

Table 12. Summary of Incidence of AEs by Year Reported in the Cosmetovigilance System for Ecamsule Containing Products

Years	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
%	0.011	0.0042	0.002	0.0029	0.004	0.0067	0.0048	0.0056	0.0095	0.0078	0.0045

In the database, there have been a total of 3444 spontaneous adverse event reports in children reported through 2003. The database defines children as individuals 16 years of age and younger. Over a ten year period, the incidence of adverse events among children is 0.0148% with 148 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 13.

Table 13. 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 1993-2003*	Incidence of children's AEs per million units sold 1993-2003**	Frequency of AEs as % of all reported AEs in adults through 2003	Frequency of AEs among children as % of all children's AEs through 2003
	Number of AEs and % of units sold for each subgroup		Number of AEs as % of all AEs in each subgroup	
All adverse events	55 (0.0055)	148 (0.148)	100%	100%
Erythema	11.8 (0.0012)	39.9 (0.0040)	21.5	27.0
Dermatitis	10.6 (0.0011)	37.1 (0.0037)	19.2	25.1
Skin Discomfort	8.0 (0.00080)	10.4 (0.0010)	14.5	7.00
Pruritus	6.6 (0.00066)	19.6 (0.0020)	12.1	13.2
Edema Skin	4.7 (0.00047)	17.1 (0.0017)	8.40	11.6
Irritation	3.6 (0.00036)	4.9 (0.00049)	6.50	3.30
Dry Skin	2.0 (0.00020)	4.5 (0.00045)	3.60	3.00
Desquamation	1.3 (0.00013)	1.2 (0.00012)	2.30	0.84
Eczema	1.4 (0.00014)	2.6 (0.00026)	2.50	1.70
Allergic Local Reaction	1.0 (0.00010)	1.1 (0.00011)	1.80	0.75
Conjunctivitis	0.90 (0.00009)	0.73 (0.00007)	1.60	0.49
Photosensitivity	0.62 (0.00006)	0.56 (0.00006)	1.10	0.38
Lacrimation Disorder	0.54 (0.00005)	0.64 (0.00006)	0.97	0.44
Skin Burn	0.57 (0.00006)	1.7 (0.00017)	1.00	1.10
Sunburn	0.36 (0.00004)	1.4 (0.00014)	0.65	0.93
Urticaria	0.32 (0.00003)	2.3 (0.00023)	0.58	1.60
Skin Discoloration	0.20 (0.00002)	0.38 (0.00004)	0.37	0.26
Acne	0.18 (0.00002)	0.04 (0.000004)	0.32	0.03
Edema Conjunctival	0.16 (0.00002)	0.94 (0.00009)	0.28	0.64

b(4)

Comments:
There are several deficiencies in the L'Oreal cosmetovigilance database. The causality of the AEs in relation to the drug/cosmetic product was not assessed. The estimate of the incidence or frequency of AEs in pediatric/adolescent population is flawed. Denominator to asses the incidence in pediatric population, chosen by the sponsor, is the number of adolescent products sold. It is not known if only adolescent products were used by children. Also we don't know if adolescent products were used by adults. Therefore, the sponsor's estimate of the incidence of AEs in children based on the total number of adolescent products sold may not be accurate.

Since the cosmetovigilance system was designed for postmarketing surveillance of cosmetic products, the criteria of serious adverse events have not been entered into the database. For the purpose of this NDA, a retrospective search was conducted by the sponsor to look for potentially serious cases. A total of six serious adverse events were discovered. Brief description of those events is presented below:

- One spontaneous report was considered serious (anaphylactic reaction) by the reporting physician and a causal relationship cannot be ruled out. A 43-year woman in Singapore experienced an anaphylactic reaction (puffy eyelids, tightness of chest and throat) 15

minutes after her first application of [redacted] Cream, containing ecamsule, [redacted] No concomitant treatment was given, and the reaction resolved within 2 hours. b(4)

- Case #11548. A 12 year old female developed redness and edema 12 hours after using the ecamsule-containing product. The subject was hospitalized for 2 days and treated with a topical steroid. No patch testing was done but a relationship to ecamsule cannot be ruled out.
- Case #17718. A 7 year old child, with a history of asthma, experienced breathing difficulties and swelling of the face and eyes four hours after applying the product. The child was treated with a nebulizer and antihistamines and was detained for 5 hours in the hospital. A dermatologist was consulted and suggested the reaction may have been to the nuts she ate for lunch. Given the multifactorial nature of her medical history and the timing of the reaction, a causal role of the sunscreens is unlikely but cannot be ruled out.
- Subject # 17614-GBC experienced an urticarial reaction two days after using an ecamsule-containing sunscreen. She was hospitalized and treated with antihistamines and steroids. A relationship to use of the ecamsule-containing sunscreen is possible.
- Case # 17846-GBC. An 8 year old child applied an ecamsule-containing sunscreen in the morning at 8:30 and by 3:00 pm developed a swollen face and eyes and a rash over the entire body. The child was hospitalized 24 hours and treated with steroids. The child had a history of eczema and had used the product one year earlier without reaction. A relationship is possible given the timing of the reaction, but a specific ingredient cannot be incriminated due to the absence of patch testing.
- Case #19642-GBC. A 5 year old female used Ambre Solaire IP 25 for the first time and developed swollen eyes, sore throat, and a raised rash involving her torso, arms and bottom. The child was taken to a doctor who prescribed penicillin and Piriton. On the evening of the same day, she experienced generalized swelling, including her tonsils. The subject was taken to the hospital and treated with penicillin, Piriton, and steroids. Five days later Ambre Solaire IP 25 was again applied to the child's body and the child's eyes again became swollen. The sponsor assessed a relationship to the ecamsule-containing sunscreen as unlikely, and related the symptoms to infectious strep throat. In the opinion of this reviewer, a relationship to the ecamsule-containing sunscreen is still probable.

The incidence of AEs associated with the use of ecamsule-containing drug products (55 per million units sold) is similar to that of avobenzone, the UV filter most recently recognized/proposed as safe and effective for use in an OTC Drug Product (sunscreens). The incidence of adverse events reported for avobenzone in the Federal Register Notice was 0.0067% of units sold (or 67 adverse events per million units sold). This was based on [redacted] units sold over a three year period. b(4)

Comment:

Postmarketing AEs reported to the sponsor did not reveal any serious safety issues. The most common AEs in the postmarketing database are consistent with the AE profile from the clinical trials.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

A total of 2539 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens.

7.2.1.1 Study type and design/patient enumeration

A list of all clinical studies to support safety is presented in Table 14 below.

Table 14. List of Studies to Support Safety

	Study #	Study Type	# of subjects
Phase 1 Local Tolerance Studies	PEN.110.01	Repeat insult patch	223
	PEN.210.01	Photoallergy	137
	PEN.250.01	Phototoxicity	26
	1.GC.03.SRE.2604	Contact sensitization and irritancy	225
	1.CG.03.SRE.2605.R01	Phototoxicity	30
	1.CG.03.SRE.2606	Photoallergy	118
Phase 1 Pharmacokinetic Studies	1.CG.03.SRE.2607	Maximized exposure PK	6
	V99.1203	Dermal absorption	5
	V3156	Urinary excretion after repeat application	8
Phase 2 Combination Policy Studies	PEN.810.05	SPF	50
	PEN.810.06	SPF	100
	PEN.910.02	UVA	70
Phase 3 UVA/AVB Protection Studies	PEN.810.01	SPF	21
	PEN.810.02	SPF	20
	PEN.820.01	SPF	21
	PEN.820.02	SPF	25
	PEN.910.01	UVA	32
	PEN.920.01	UVA	14
	PEN.99001.01COS	SPF	24
Phase 3 Long-Term Studies	PEN.750.01	12 Months Clinical Safety	248
	PEN.750.02	12 Months Clinical Safety	246
	PEN.750.03	12 Months Clinical Safety	79
	RD.06.SRE.18047	Clinical safety ——	475
Other Supportive Studies	PEN.570.01	Acnegenicity/comedogenicity	44
	PEN.570.02	Comedogenicity	30
	PEN.1010.01	Moisturization	32
Other Formulations Containing Ecamsule	RD.06.SRE.18057	Efficacy/Safety	144
	RD.06.SRE.2616	Efficacy/Safety	86

b(4)

Studies evaluating safety of the [redacted] have been previously evaluated by the reviewers in HFD-540. Therefore, studies with [redacted] are not being discussed in detail in this review. b(4)

7.2.1.2 Demographics

7.2.1.2.1 Phase 1, 2, and 3 Clinical Studies

Subject demographics and baseline characteristics across the Phase1, 2, and 3 clinical studies were similar (Table 15). The majority of subjects were Caucasians, middle-aged females, except in the pharmacokinetic studies where subjects were male and slightly younger. The predominant skin type was type II (sensitive skin) and III (normal skin), with no evidence of active skin abnormalities.

Classification of the skin phototypes:

- Type I – always burns easily; never tans
- Type II – always burns easily; tans minimally
- Type III – burns minimally; tans gradually
- Type IV – burns minimally; always tans well
- Type V – rarely burns; tans profusely
- Type VI – never burns; deeply pigmented

Table 15. Demographic and Baseline Characteristics of Subjects in Phase 1, 2, & 3 Clinical Studies

	N	Mean Age	Gender	Race	Major Skin Type
Phase 1 Local Tolerance Studies					
PEN.110.01	223	48 (18-91)	74% female	82% Caucasian	31% type III
PEN.210.01	137	43 (16-68)	77% female	93% Caucasian	58% type III
PEN.250.01	26	40 (18-63)	85% female	81% Caucasian	73% type III
1.GC.03.SRE.2604	225	43 (16-85)	68% female	100% Caucasian	52% type III
1.CG.03.SRE.2605.R01	30	28 (18-53)	73% female	100% Caucasian	70% type II
1.CG.03.SRE.2606	118	33 (18-62)	64% female	100% Caucasian	66% type II
Phase 1 Pharmacokinetic Studies					
1.CG.03.SRE.2607	6	37 (23-55)	100% male	100% Caucasian	83% type III
V99.1203	5	22 (19-29)	100% male	Not specified	Not done
V3156	8	26 (19-41)	100% male	100% Caucasian	Not done
Phase 2 Combination Policy Studies					
PEN.810.05	50	36 (18-65)	68% female	96% Caucasian	72% type II
PEN.810.06	100	37 (18-63)	66% female	99% Caucasian	57% type II
PEN.910.02	70	35 (18-62)	57% female	77% Hispanic	50% type III&IV
Phase 3 UVA/AVB Protection Studies					
PEN.810.01	21	43 (26-58)	95% female	100% Caucasian	XX% type III
PEN.810.02	20	38 (18-52)	56% female	100% Caucasian	96% type III
PEN.820.01	21	43 (26-58)	95% female	100% Caucasian	71% type III
PEN.820.02	25	38 (18-52)	56% female	100% Caucasian	56% type III
PEN.910.01	32	42 (18-65)	53% female	66% Caucasian	63% type III
PEN.920.01	14	47 (35-65)	86% female	100% Caucasian	79% type III
PEN.99001.01COS	24	33 (19-47)	75% female	100% Caucasian	46% type III

7.2.1.2.2 Phase 3 Long-Term Safety Studies

FDA requested that the sponsor enroll 100 children, 6 months to 12 years of age, in PEN.750.03 and 100 children between 6 months and 12 years of age in PEN.750.02. Only 64 children were included in the safety population in PEN.750.03. However, 179 children 6 months to 12 years of age (73% of all subjects) were enrolled and 69% of them (124/179) completed PEN.750.02. PEN.705.02 was conducted on the (b) (4) SPF 15 lotion formula (760-006). The demographic and baseline characteristics for subjects in the long-term safety studies are presented in Table 16 below.

Table 16. Demographics and Baseline Characteristics for Subjects in the Long-Term Safety Studies

Characteristic		Study PEN.750.01 N=248	Study PEN.750.02 N=246	Study PEN.750.03 N=79	Study 18047 N=475
Age (years)	Mean	35.79 (19.37)	10.98 (12.56)	8.69 (12.05)	45.6 (13.48)
	Median	35.44	6.69	3.69	46.0
	Range	12.04-83.43	0.5-67.95	0.64-48.15	12-85
Age group (years)	> 0.5 to ≤ 2	0 (0)	57 (23.17)	24 (30.38)	0
	> 2 to ≤ 6	0 (0)	60 (24.39)	32 (40.51)	0
	> 6 to ≤ 12	0 (0)	62 (25.20)	8 (10.13)	0
	12 to ≤ 18	78 (31.45)	24 (9.76)	2 (2.53)	11 (2.3)
	18 to ≤ 65	145 (58.47)	42 (17.07)	13 (16.46)	428 (90.1)
	> 65	25 (10.08)	1 (0.41)	0	36 (7.6)
Gender (N[%])	Male	58 (23.39)	101 (41.06)	26 (32.91)	83 (17.5)
	Female	190 (76.61)	145 (58.94)	53 (67.09)	392 (82.5)
Race (N[%])	Caucasian	193 (77.82)	193 (78.46)	66 (83.54)	431 (90.7)
	Black	23 (9.27)	8 (3.25)	0	10 (2.1)
	Hispanic	26 (10.48)	21 (8.54)	6 (7.59)	25 (5.3)
	Asian/Pacific Islander	5 (2.02)	2 (0.81)	4 (5.06)	4 (0.8)
	Other	1 (0.40)	22 (8.94)	3 (3.80)	5 (1.1)
Skin phototype (N[%])	I	17 (6.85)	14 (5.69)	6 (7.59)	87 (18.3)
	II	52 (20.97)	96 (39.02)	27 (34.18)	179 (37.7)
	III	90 (36.29)	82 (33.33)	30 (37.97)	153 (32.2)
	IV	44 (17.74)	33 (13.41)	12 (15.19)	42 (8.8)
	V	29 (11.69)	17 (6.91)	2 (2.53)	13 (2.7)
	VI	16 (6.45)	4 (1.63)	2 (2.53)	1 (0.2)
Sensitive skin	Yes	196 (79.03)	207 (84.15)	67 (84.81)	--
	No	52 (20.97)	39 (15.85)	12 (15.19)	--
Predisposed subjects	Yes	97 (39.11)	159 (64.63)	45 (56.96)	--
	No	151 (60.89)	87 (35.37)	34 (43.04)	--
	—	0	0	0	475 (100)

Subjects enrolled into the (b) (4) studies were younger than subjects enrolled into Study RD.06.SRE.18047 — Women outnumbered men in all studies. Nearly twice as many women compared with men were enrolled in the (b) (4) studies PEN.750.01 and PEN.750.03. Slightly more women than men were enrolled in PEN.750.02 (59% women and

b(4)

41% men), and in Study RD.06.SRE.18047, the ratio of women to men was nearly 5:1 (85% women vs. 18% men).

The majority of subjects in each study were Caucasian (78% or more). Most subjects had skin phototype II or III.

The overall safety population for this integrated safety summary consisted of:

- 243 pediatric subjects 6 months to 12 years of age
- 115 adolescent subjects
- 628 adults
- 62 elderly subjects

7.2.1.2.3 Other Supportive Studies

The majority of subjects who enrolled in the supportive studies were Caucasian females with a mean age of about 40 years. The baseline and demographic characteristics of subjects in both the (b) (4) and the ——— Cream studies were similar (Table 17). b(4)

Table 17. Demographic and Baseline Characteristics of Subjects in Other Supportive Studies

Study	N	Age Mean (range)	Gender	Race	Major Skin Type
(b) (4) **Cosmetic Claim Support Studies**					
PEN.570.01	44	(18-40)*	45% female	80% Caucasian	30% type III
PEN.570.02	30	42 (20-59)	93% female	97% Caucasian	Not done
PEN.1010.01	32	41 (20-59)	66% female	84% Caucasian	Not done
Other Formulations Containing Ecamsule ——— Cream Studies)					
RD.06.SRE.18057	144	40 (18-73)	82% female	98% Caucasian	50% type II
RD.06.SRE.2616	86	41 (18-65)	92% female	100% Caucasian	41% type II

b(4)

* Mean age not provided in the report

7.2.1.3 Extent of exposure (dose/duration)

7.2.1.3.1 Phase 1, 2, and 3 Clinical Studies

Extent of exposure for subjects who participated in the Phase 1, 2, and 3 clinical studies was wide ranging, spanning from hours to weeks depending on the study design. The body surface area covered varied from patch application to whole body application. The usual amount of product applied was 2 mg/cm^2. The largest amounts of sunscreen formula applied (15 grams twice daily and 10 grams once daily) were in two pharmacokinetic studies (1.CG.03.SRE.2607 and V3156). Extent of exposure data is summarized in Table 18 below.

Table 18. Extent of Exposure for Subjects in Phase 1, 2, & 3 Clinical Studies

Study Number	N	Amount of Application	Length of Exposure
Phase 1 Local Tolerance Studies			
PEN.110.01	223	0.2 mL to sites 8 mm in diameter under occlusive conditions	4 weeks, 12-24 hrs (3 weeks); 72 hrs (3 weekends); 1-48 hrs (1 week)
PEN.210.01	137	0.2 mL to each 0.75 in x 0.75 in test site each time	24-hr applications 2x week, 3 consecutive weeks (induction phase); challenge with single 24-hr application
PEN.250.01	26	0.2 mL to each of 8 sites under occlusive conditions	Single exposure; 24 hours
1.GC.03.SRE.2604	225	50 µL under occlusive conditions	4 24-hr & 1 72-hr applications/week, 3 weeks; 1 48-hr application after 2-week rest period
1.CG.03.SRE.2605.R01	30	50 µL of product	24 hours
1.CG.03.SRE.2606	118	50 µL of product	Twice daily for 3 weeks + 1 single dose
Phase 1 Pharmacokinetic Studies			
1.CG.03.SRE.2607	6	15 g applied twice daily 9 days	18 whole body applications
V99.1203	5	0.2 g ([^{14}C]-ecamsule, 2%) 100 cm^2 area	4 hours on volar forearm
V3156	8	10 g, 4.95% ecamsule	5 consecutive days
Phase 2 Combination Policy Studies			
PEN.810.05	50	100 mg	Single exposure; 22-24 hours
PEN.810.06	100	100 mg	Single exposure; 22-24 hours
PEN.910.02	70	70 mg	Single exposure; 3 hours
Phase 3 UVA/UVB Protection Studies			
PEN.810.01	21	120 mg	Single exposure; 22-24 hours
PEN.810.02	20	100 mg	Single exposure; 22-24 hours
PEN.820.01	21	120 mg	Single exposure; 22-24 hours
PEN.820.02	25	100 mg	Single exposure; 22-24 hours
PEN.910.01	32	70 mg	Single exposure; 22-24 hours
PEN.920.01	14	100 mg	Single exposure; 72 hours
PEN.99001.01COS	24	100 mg	Single exposure; 22-24 hours

7.2.1.3.2 Phase 3 Long-Term Safety Studies

Exposure to study treatments for subjects enrolled in the four long-term safety studies is summarized in Table 19.

Table 19. Summary of Treatment Duration, Study Drug Use and Product Application in the Long-Term Safety Studies

		PEN.750.01 N=248	PEN.750.02 N=246	PEN.750.03 N=79	Study 18047 N=475
Treatment Duration (days)	N	248	246	79	475
	Mean (SD)	307.1 (110.3)	88.4 (96.9)	37.3 (34.3)	258.3 (125.8)
	Median	356.0	44.5	31.0	335.0
	Range	1.0-376.0	1.0-363.0	1.0-225.0	1.0-393.0
Total Usage (g)	N	237	237	74	445
	Mean (SD)	570.6 (474.0)	256.6 (249.9)	143.0)106.8)	302.3 (297.4)
	Median	433.4	174.5	122.0	211.6
	Range	27.9-3141.8	0.1-1650.8	6.8-532.0	-1.5-2006.0
Daily Usage (g/day)	N	235	235	72	445
	Mean (SD)	2.0 (2.6)	4.2 (3.6)	4.8 (4.5)	1.3 (1.9)
	Median	1.6	3.1	3.7	0.9
	Range	0.16-35.5	0.07-26.85	0.86-29.6	-1.0-26.1
Product Application (total number)	N	239	237	75	453
	Mean (SD)	417.4 (180.0)	145.9 (295.2)	55.9 (55.5)	303.1 (171.3)
	Median	388.0	57.0	42.0	342.0
	Range	1.0-1029.0	1.0-2687.0	0.0-421.0	1.0-1158.0
Daily Application (number/day)	N	239	237	73	453
	Mean (SD)	1.3 (0.4)	1.4 (0.8)	1.5 (0.5)	1.1 (0.4)
	Median	1.1	1.2	1.3	1.1
	Range	0.95-3.01	1.0-7.78	1.0-2.8	0.01-3.0

Total amount of study medication used was highest for the daily-use study PEN.750.01 (570.6 grams) followed by study RD.06.SRE.18047 (301.3 grams), PEN.750.02 (256.6 grams) and PEN.750.03 (143 grams). Daily usage in grams was highest for (b) (4) studies PEN.750.02 and PEN.750.03 (4.2 grams and 4.8 grams, respectively). On the days that subjects used sunscreen treatment, the number of applications was similar for subjects in all studies (1.1 to 1.5 applications/day).

Comment:
The reasons why the usage of sunscreen was so different in these long-term studies, could be explained by differences in directions for use. In study PEN.750.0, subjects were instructed to apply the lotion to the face, neck, and arms daily. In studies PEN.750.02 and PEN.750.03, subjects were instructed to apply the product to all sun-exposed areas and to reapply as needed during extended outdoor usage.

The average length of treatment for all studies combined was 213 days and ranged from 1 to 393 days. Exposure to study treatment for all subjects (N=1048) in the long-term safety studies combined by duration of treatment was as follows:

- 473 subjects treated for 1 to <180 days (average 62.5 days)
- 340 subjects treated for 180 to <360 days (average 315.9 days)
- 235 subjects treated for more than one year (average 368.2 days)

Treatment duration assessed for age subgroups in three long-term studies (750.01, 750.02, and 750.03), revealed that the pediatric age subgroups had the shortest treatment duration (Table 20).

Table 20. Treatment Duration for Different Age Groups (three long-term studies)

Age groups	Mean	SD	Median	Range
0.5 to ≤ 2 years (N=81)	57.79	68.92	31.0	1-312
2 to ≤ 6 years (N=92)	67.45	80.32	36.0	1-363
6 to ≤ 12 years (N=70)	87.59	99.05	37.5	1-350
12 to ≤ 18 years (N=104)	247.67	145.40	344.0	1-371
18 to ≤ 65 years (N=200)	250.24	142.51	346.0	1-376
> 65 years (N=26)	308.31	117.58	360.5	2-372

In study PEN.750.02, each subject was to plan for at least 14 days with outdoor activities, such as a beach vacation or weekend gardening or sport activities, where the use of a sunscreen was required. A total of 14.2% of the study PEN.750.02 population did not use study drug for the required 14 days and also did not have the 14 days of sun exposure required by the protocol.

7.2.1.3.3 Other Supportive Studies

A wide range of exposure times and applications were observed in the supportive studies. Table 21 summarizes data on extent of exposure in the five supportive studies.

Table 21. Extent of Exposure for Subjects in the Other Supportive Studies

Study Number	N	Amount of Application	Length of Exposure
(b) (4) **Cosmetic Claim Support Studies**			
PEN.570.01	44	Entire face (excluding lips and eye area), twice daily	6 weeks
PEN.570.02	33	0.3 mL/300mg topically to sites 3cm x 3cm (total 12 applications)	4 weeks, 48-72 hours each application
PEN.1010.01	32	80 mg on volar forearm	Single exposure; 24 hours
Other Formulations Containing Ecamsule [redacted] **Cream Studies)**			
RD.06.SRE.18057	144	Median 7g (range 5-11)	To whole body for 6 days
RD.06.SRE.2616	86	Median 8-9g (range 6.7-12)	To whole body for 6 days

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Safety data submitted from the literature is discussed in section 8.6 of this review.

7.2.3 Adequacy of Overall Clinical Experience

A long marketing experience in foreign countries, in addition to several clinical studies, does not reveal any serious safety signals for ecamsule-containing drug products. Data supports the safety of these products for over-the-counter marketing.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Adequacy of preclinical data is being assessed by pharmtox reviewers. Refer to disciple-specific reviews.

7.2.5 Adequacy of Routine Clinical Testing

The sponsor has conducted all the required studies requested by FDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsor has submitted all the required data to characterize the pharmacological profile of this combination product. Studies to support the contribution of each ingredient to the efficacy of the products are being reviewed by the interdisciplinary scientist in the Office of Nonprescription Products.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

From a clinical safety perspective, a study in pregnant women is recommended (see section 7.1.14 of this review).

The need for studies in children below 6 months of age will be addressed by the Division of Pediatric Development.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, this application is adequate for approval but not complete.

7.2.9 Additional Submissions, Including Safety Update

A four-month safety update was submitted by the sponsor as required by 21 CFR 314.50 (d)(5)(vi)(b). The sponsor states that there were no new animal, non-clinical or clinical studies initiated or completed with the three-active ingredients in (b) (4) formulations after submission of NDA 21-501 and NDA 21-502 on May 16, 2005. There was no additional information in the literature on adverse reactions to ecamsule since reporting date of October 2004 in the NDA 21-501 through August 31, 2005. Therefore, the safety update included only global cosmetovigilance data on formulas containing the new chemical entity, ecamsule. Since the sponsor did not analyze this updated safety information separately, it was incorporated into the postmarketing experience section of the review (see Section 7.1.17).

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

A total of 2539 subjects were exposed at least once to an ecamsule-containing sunscreen product during the development phase of these sunscreens. It is inappropriate to combine safety data from all the clinical studies because of differences in formulations and design and methodology used in different studies.

7.4.1.1 Pooled data vs. individual study data

For the incidence of AEs in individual studies see section 7.1.5 of the review.

7.4.1.2 Combining data

Only data gathered during the three (b) (4) and one [redacted] long-term studies were combined to assess the predictive factors. A total of 1048 subjects participated in those four studies. b(4)

7.4.2 Explorations for Predictive Factors

Analyses of safety data were performed for patient-predictive factors such as demographics, skin phototype, and duration of product use. Since drug-related adverse events were limited to skin, only dermatological AEs are discussed in this part of the review.

7.4.2.1 Explorations for dose dependency for adverse findings

There was no assessment of dose dependency performed.

7.4.2.2 Explorations for time dependency for adverse findings

Table 22 below provides a comparison of related dermatological adverse events for subjects in all four long-term studies combined and by treatment duration.

Table 22. Comparison of Treatment-Related Dermatological AEs for Subjects in All Four Long-Term Studies Combined and by Treatment Duration

		Treatment duration			
		1 to <180 days (N=473)	180 to <360 days (N=340)	≥360 days (N=235)	All subjects combined (N=1048)
Subjects with at least 1 AE		295 (62.4)	244 (71.8)	182 (77.4)	721 (68.8)
Subjects with at least 1 TRAE		44 (9.3)	53 (15.6)	50 (21.3)	147 (14.0)
Subjects with at least 1 skin and appendage AE		137 (29.0)	136 (40.0)	102 (43.4)	375 (35.8)
Subjects with at least 1 skin and appendage TRAE		41 (8.7)	49 (14.4)	46 (19.6)	136 (13.0)
Skin Conditions	Acne	4 (0.8)	8 (2.4)	9 (3.8)	21 (2.0)
	Eczema	1 (0.2)	2 (0.6)	2 (0.9)	5 (0.5)
	Seborrhea	0 (0)	1 (0.3)	1 (0.4)	2 (0.2)
	Folliculitis	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
	Rosacea	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Skin neoplasm	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Pimples	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Herpes simplex	0 (0)	0 (0)	1 (0.4)	1 (0.1)
	Hirsutism	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Miliaria	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Dermatitis/ Irritation	Dermatitis	6 (1.3)	8 (2.4)	2 (0.9)	16 (1.5)
	Irritant dermatitis	4 (0.8)	1 (0.3)	4 (1.7)	9 (0.9)
	Irritation skin	2 (0.4)	1 (0.3)	2 (0.9)	5 (0.5)
	Skin irritation	2 (0.4)	0 (0)	0 (0)	2 (0.2)
	Allergic contact dermatitis	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Irritant contact dermatitis	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Photosensitization	Photosensitivity rash	4 (0.8)	4 (1.2)	10 (4.3)	18 (1.7)
	Photosensitivity	0 (0.0)	0 (0)	3 (1.3)	3 (0.3)
	Photoallergic reaction	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Inflammation	Sunburn	6 (1.3)	4 (1.2)	7 (3.0)	17 (1.6)
	Erythema	4 (0.8)	3 (0.9)	3 (1.3)	10 (1.0)
	Skin infection	0 (0)	2 (0.6)	0 (0)	2 (0.2)
	Skin edema	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Dry/Oily Skin	Dry skin	1 (0.2)	8 (2.4)	2 (0.9)	11 (1.0)
	Desquamation	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Oily skin	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Dryness skin	0 (0)	0 (0)	2 (0.9)	2 (0.2)
	Drying	1 (0.2)	0 (0)	0 (0)	1 (0.1)
Skin Sensation	Pruritus	3 (0.6)	4 (1.2)	1 (0.4)	8 (0.8)
	Itching skin	2 (0.4)	5 (1.5)	1 (0.4)	8 (0.8)
	Skin discomfort	0 (0)	4 (1.2)	1 (0.4)	5 (0.5)
	Discomfort skin	1 (0.2)	0 (0)	1 (0.4)	2 (0.2)
	Stinging sensation	2 (0.4)	0 (0)	1 (0.4)	3 (0.3)
	Burning sensation skin	1 (0.2)	1 (0.3)	0 (0)	2 (0.2)
Skin Coloration	Skin discoloration	0 (0)	1 (0.3)	0 (0)	1 (0.1)
	Discoloration skin	0 (0)	0 (0)	1(0.4)	1 (0.1)
	Blotching	1 (0.2)	0 (0)	0 (0)	1 (0.1)
	Hyperpigmentation skin	0 (0)	0 (0)	1 (0.4)	1 (0.1)

With a few exceptions (acne, photosensitivity and sunburn), most subjects reported treatment-related dermatological AEs during the first 360 days of treatment. Acne and photosensitivity were reported more often by subjects treated for a longer time intervals.

7.4.2.3 Explorations for drug-demographic interactions

No formal drug-demographic interaction studies have been performed on any of the (b) (4) formulas. Across the four long-term clinical studies used in support of safety, skin phototypes (Type I – Type VI), age (6 months to no upper limit), race, gender, and sensitive versus non-sensitive type subgroups have been represented. Subjects with AEs in each subgroup were summarized by numbers and percentages in each individual clinical study report. The sponsor did not provide combined data drug-demographics interactions for all four long term studies. Therefore, table 23 summarizes treatment related adverse events in the three (b) (4) long-term studies by demographics.

Table 23. Treatment Related AEs by Demographics in the Three (b) (4) Long-Term Studies

		Drug Related AEs	
Demographic Subgroup		**Dermatological**	**Non-Dermatological**
Gender	Males (N=185)	21 (11.4%)	1 (0.5%)
	Females (N=388)	33 (8.5%)	7 (1.8%)
Race	Asian (N=11)	2 (18.2%)	0 (0.0%)
	Black (N=31)	7 (22.6%)	1 (3.2%)
	White (N=452)	38 (8.4%)	5 (1.5%)
	Hispanic (N=53)	7 (13.2%)	0 (0.0%)
	Other (N=26)	0 (0.0%)	0 (0.0%)
Skin Phototype	Type I (N=37)	0 (0.0%)	0 (0.0%)
	Type II (N=175)	23 (13.1%)	3 (1.7%)
	Type III (N=202)	19 (9.4%)	3 (1.5%)
	Type IV (N=89)	5 (5.6%)	1 (1.1%)
	Type V (N=48)	5 (10.4%)	0 (0.0%)
	Type VI (N=22)	2 (9.1%)	1 (4.5%)
Age	0.5 to ≤ 2 yrs (N=81)	3 (3.7%)	1 (1.2%)
	> 2 to ≤ 6 yrs (N=92)	8 (8.7%)	0 (0.0%)
	> 6 to ≤ 12 yrs (N=70)	5 (7.1%)	0 (0.0%)
	> 12 to ≤ 18 yrs (N=104)	7 (6.7%)	0 (0.0%)
	> 18 to ≤ 65 yrs (N=200)	30 (15.0%)	6 (3.0%)
	> 65 yrs (N=26)	1 (3.8%)	1 (3.8%)

Even though number of subjects in some of the demographic subgroups was low, there was no obvious difference in the incidence of drug related adverse events among subgroups of subjects with different skin phototypes, race, gender, and skin sensitivity.

For the three combined (b) (4) long-term studies, 60 of the 573 subjects (10.5% incidence) reported treatment-related adverse events and 54 (90%) of them were dermatologic. Of these, 17 were reported by pediatric subjects. Subjects in the youngest pediatric subgroup experienced the lowest incidence (3.7%) of treatment related dermatologic adverse reactions. There were 3 events among 81 children, ages 6 months and 2 years. Among 2 to 6 year old children, the incidence was 8.7% (8 events among 92 children) closely followed by an incidence of 7.1%

(5/70 subjects) among 6 to 12 year olds, and an incidence of 6.7% (7/140) among adolescents. In the adults, the incidence of treatment related dermatologic AEs was considerably higher, 15%. On average, adult subjects used sunscreens for longer treatment durations than pediatric subjects because most adults participated in the 12 months daily use study. The difference in adverse event incidence rates between children and adults may be related to differences in duration of use.

There did not appear to be a specific association of adverse reactions with pediatric use of the sunscreens.

The sponsor submitted pediatric adverse events spontaneously reported to the L'Oreal Cosmetovigilance System following use of sunscreens containing any (b) (4) sunscreen ingredients (octocrylene, Mexoryl SX, avobenzone, and titanium dioxide). There were a total of 386 adverse event reports in children aged 1 to 16 years between 1996, when the products were first marketed, and 2004. Distribution of AEs by age is as follows:

- 81% of the children were 7 years-old or younger
- 15% of the children were older than 7 years
- 4% were unidentified

The number of reports per year is as follows:

1996 - 1
1997 - 9
1998 - 11
1999 - 35
2000 - 40
2001 - 61
2002 - 49
2003 - 78
2004 - 102

Despite some fluctuations there is a trend towards a gradual increase in the number of reactions that the sponsor associates with an increase in use of sunscreen products during this time.

In the majority of cases, reactions occurred within several hours after first application, and the majority resolved in less than 3 days. No permanent sequelae were reported. All of the reactions were limited to the sunscreen application site. The predominant manifestation was erythema (74% of cases), followed by papules (49%), edema (32%), dryness (8%), "eczema" (6%), urticaria-like lesions (2%). These manifestations were accompanied by pruritus in 35% and by "burning sensation" in 6% of cases.

Comments:
From the available clinical and post-marketing data, it does not appear that pediatric patients are more likely to develop cutaneous adverse reactions than adults. There were no unusual adverse events noted in children exposed to the sunscreen products containing ecamsule.

7.4.2.4 Explorations for drug-disease interactions

No analysis on drug-disease interactions was performed for any study. All studies were performed on healthy individuals with no histories of allergy to product ingredients or active severe systemic cutaneous allergic conditions such as dermatitis, eczema, or psoriasis.

(b) (4) sunscreen products should be applied only to healthy skin. However, sometimes it may be administered inadvertently to individuals with abnormal skin conditions. This situation is exemplified by one study, (b) (4) 750.03, where a 14-month-old boy with a history of eczema, was enrolled and developed a "flare-up" of eczema on the back of his neck while in the study. Upon application of the sunscreen product, the eczema worsened. The event was considered mild and possibly related to study medication. Following treatment with topical hydrocortisone, the event resolved. The sunscreen was not re-applied to the neck area but was used on other parts of his body. No further sequelae were observed.

— studies RD.06.SRE.18047, RD.06.SRE.18057, and RD.06.2616 enrolled subjects with a demonstrated history of — When not undergoing a flare-up, these subjects were considered to have "normal" skin. The adverse events reported by subjects in these studies did not indicate a new, emergent pattern of adverse events unique to individuals with — The presence of — in the subject population did not change the safety profile of the study treatments in these predisposed subjects.

b(4)

The sponsor analyzed the incidence of adverse events reported among a subgroup of predisposed subjects (those with a history of or current atopic/dry skin, asthma/allergy, acne/rosacea, and/or sensitive skin) who participated in the three long-term (b) (4) studies. A higher incidence of adverse events was reported for the predisposed subjects (69.1%) than for subjects without a predisposing medical condition (59.5%). The incidence of treatment-related AEs was also higher in subjects with predisposing conditions (12.9%) than subjects without them (10.5%). The majority of treatment-related adverse events were dermatological, and all were mild or moderate in severity.

Table 24. Treatment Related AEs in the Three (b) (4) Long-Term Studies by Predisposing Conditions

	Drug Related AEs	
Predisposing Conditions	**Dermatological**	**Non-Dermatological**
Asthma/Allergy (N=106)	22 (20.8%)	1 (0.9%)
Atopic/Dry Skin (N=75)	13 (17.3%)	2 (2.7%)
Acne/Rosacea (N=99)	11 (11.1%)	1 (1.0%)
Sensitive Skin (N=103)	12 (11.7%)	5 (4.9%)
All predisposed subjects (N=272)	32 (11.8%)	5 (1.8%)

Comment:
Subjects with predisposing dermatological conditions had a higher incidence of cutaneous adverse event. The proposed label appropriately directs consumers to stop use the product if rash or irritation develops and lasts. Labeling should also carry a warning to use caution when applying the sunscreen on damaged skin.

7.4.2.5 Explorations for drug-drug interactions

No formal drug-drug interaction studies have been conducted with (b) (4) formulations. The sponsor states, that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin, and therefore, it is unlikely that interactions with systemic medications would occur.

7.4.3 Causality Determination

The sponsor has not performed special causality assessments. None of the clinical studies conducted to support the two combination sunscreen drug products had a control group.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing directions for (b) (4) 15 WR lotion are:

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

b(4)

The proposed dosing directions for (b) (4) 15 lotion are:

- apply evenly ——— before sun exposure
- children under 6 months of age: ask a doctor

Both of the proposed dosing directions are consistent with the TFM for Sunscreen Drug Products for OTC Human Use.

8.2 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with (b) (4) formulations. The sponsor states, that ecamsule and its combination formulations are poorly absorbed (<1%) when topically applied to the skin, and therefore, it is unlikely that interactions with systemic medications would occur. Subjects who participated in the clinical trials were allowed to use any systemic or topical treatments. There were no safety signals noted due to a particular drug-drug interaction.

8.3 Special Populations

These products are indicated for healthy individuals. One safety concern that surfaced from the available clinical data is the use of sunscreens in subjects with predisposing dermatological conditions. As discussed in section 7.4.2.4 of this review, the labeling for the products should carry a warning to use caution when applying the sunscreen on damaged skin.

8.4 Pediatrics

The sponsor is requesting 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.

During the end-of-phase 2 meeting, FDA asked the sponsor to include children six months and older in the study PEN.750.02, and recommended that at least 50% of the subjects be below 12 years of age. In addition, FDA recommended including children ages 6 months to 12 years in both studies PEN.750.01 [redacted] As an alternative to the pediatric [redacted] Only 64 children were included in the safety population in PEN.750.03. However, 179 children 6 months to 12 years of age (73% of all subjects) were enrolled and 69% of them (124/179) completed PEN.750.02. b(4)

Safety of the two sunscreen lotions in pediatric populations has been discussed in section 7.4.2.3 of this review. A total of 243 children 6 months to 12 years old participated in the (b) (4) long term use clinical trials. There were no children under 12 years old included in the daily use study PEN.750.01. Of 79 subjects in intermittent use study PEN.750.03, 64 children 6 months to 12 years of age (81% of all subjects, 55 pediatrics completed the study) were included in the safety population. Additionally, in intermittent use study PEN.750.02, 179 children 6 months to 12 years of age (73% of all subjects) were enrolled and 69% (124/179) of these children completed the study. While PEN.750.02 was conducted on a different (b) (4) formula (760-006) than the two (b) (4) formulations being reviewed (see section 4.1, Table 1), it contained a higher concentration of the new chemical entity, ecamsule, than did 539-009 used for PEN.750.03.

Ecamsule has been marketed for children in Europe since 1996. In the opinion of this reviewer, there is an adequate extent of exposure and no unusual safety signals noted in the pediatric population down to 6 months of age.

It is unclear whether safety or efficacy data are needed for these new sunscreen products in children below 6 months of age. Clinical practice guidelines published by the American Academy of Pediatrics (AAP)[2] do not recommend using sunscreens in children less than 6 months of age for the following reasons:

1. Since children of this age are not mobile and cannot remove themselves from uncomfortable light and heat, they should be kept out of direct sunlight, in a shade.
2. Many infants have impaired functional sweating. Exposure to the heat of the sun may increase the risk of heatstroke.
3. Sunburn may occur readily because an infant's skin has less melanin than at any other time in life.
4. Concerns are raised that human skin under 6 months may have different absorptive characteristics; biologic system systems that metabolize and excrete drugs may not be fully developed.

[2] American Academy of Pediatrics. Ultraviolet Light: A Hazard to Children. Pediatr 1999;104(2): 328-333

AAP further states that, it may be reasonable to apply sunscreen to small areas, such as face and the back of the hands when infant's skin is not protected adequately by clothing.

In the opinion of this reviewer, the two sunscreen lotions should be labeled as requested by the sponsor for the use in children six months and older. The need for pediatric studies will be also addressed by the Division of Pediatric Development.

8.5 Advisory Committee Meeting

There is no advisory committee meeting planned for these two NDAs.

8.6 Literature Review

The sponsor conducted a scientific literature search on all three active sunscreen ingredients:

- for ecamsule, up to 2004
- for octocrylene, from 1999 (TFM publication) to 2004, and
- for avobenzone, from 1995 up to 2004

The following databases were used for the search: Medline, Embase, Biosis, Toxline, Hazardous Substances Data Bank, ToxFile, CancerLit, Pascal, HSELINE (Health and Safety), Allied and Complimentary Medicine, CA Search (Chemical Abstracts), and Global Health. Only articles, where safety of these three sunscreen ingredients is discussed, are summarized below.

Ecamsule
No major side effects associated with the use of ecamsule-containing sunscreens have been identified by the sponsor in the scientific literature. Two articles (References 1 & 2) reported studies evaluating photosensitivity of different drug and cosmetic products and other environmental allergens. Ecamsule-containing cosmetic sunscreens were tested and were found to be photosensitizing photoallergens.

Octocrylene
One article (Reference 3) reported two cases of photoallergic dermatitis associated with the use of products containing octocrylene.

Avobenzone
A total of seven articles (References 4 through 10) reported photoallergies and one article (Reference 11) reported allergic contact dermatitis associated with use of sunscreen products containing avobenzone.

Comments:
Photoallergic reactions to sunscreens are well known and documented in medical literature. These reactions are rare and most often related to the individual sensitivity of the subject. Many individuals, who reported photoallergic reactions after sunscreen use, had contact or photo allergies to several other medications or cosmetic products. Potential for irritation, contact

sensitization, phototoxicity or photosensitization will be addressed by the reviewer in the Division of Dermatological and Dental Drug Products.

8.7 Postmarketing Risk Management Plan

There is no postmarketing management plan.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety profile of ecamsule-containing sunscreen ingredient in combination with other three monograph sunscreen ingredients is acceptable for OTC marketing.

9.2 Recommendation on Regulatory Action

The proposed (b) (4) SPF 15 W/R lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 3%) and (b) (4) SPF 15 lotion (Avobenzone 2%+Octocrylene 10%+Ecamsule (Mexoryl®) 2%) have an acceptable safety profile, and therefore, are approvable for OTC marketing from the safety stand point. Final approvability depends on the outcome of the efficacy, preclinical, and chemistry data, which are being reviewed by other reviewers.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

If these NDAs are approved, a controlled study in pregnant women should be conducted to evaluate the relationship between the sunscreen exposure during pregnancy and vascular skin abnormalities in babies.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The proposed labeling for two (b) (4) sunscreen products is presented below. The labeling review is being done by the interdisciplinary scientist in the Office of Nonprescription Products. The sponsor incorporated all the important warnings for sunscreen drug products.

The sponsor should incorporate a warning to use caution when applying the sunscreen on damaged skin.

In addition to standard warnings, it is recommended to

b(4)

Based on the safety data review, labeling should not carry cosmetic claims. Studies conducted to support the are being reviewed by the reviewers in DDDDP. Final recommendations on the acceptability of those claims will be provided by the reviewers in DDDDP.

b(4)

9.4.1 Labeling

b(4)

b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

/ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

10 APPENDICES

10.1 Review of Individual Study Reports

Sections 10.1.1 through 10.1.3 will present design and methods of the three (b) (4) long-term safety studies. Combined results of these studies have been discussed already earlier in the review.

10.1.1 **PEN.750.01**. Clinical Safety Trial of "Daily-Use" (b) (4) Sunscreen (539-009) in Long-term Conditions

This was a multicenter (six centers), open-label, uncontrolled safety trial of product usage. Two hundred forty-eight (248) healthy volunteers were enrolled in the study. All 248 subjects were treated at least once with the study drug and are included in these analyses (Safety Population). The total study duration was 12 months, during which the subjects experienced periods of sun exposure.

Subjects who qualified for the study by meeting all of the inclusion/exclusion criteria were enrolled in the study and given (b) (4) Sunscreen (539-009) during the baseline visit. Also during this visit, concomitant therapy and medical history monitoring were conducted, as was a thorough dermatological examination of the face, neck, and hands. The subjects applied (b) (4) Sunscreen (539-009) to their face, neck, and hands at least once each morning after washing or cleansing. Subjects could use the sunscreen more than once daily on their face, neck, and hands, at their discretion, for periods of sun exposure. Subjects were encouraged to re-apply when needed. Other sunscreens could also have been used on other body areas during periods of sun exposure if needed. Subjects were given a diary in which they recorded daily product usage and sun exposure. All subjects were required to attend follow-up visits at the study site at Months 1, 2, 4, 6, 8, 10 and 12 for dermatological examinations, questioning about adverse events and concomitant medications, and to complete a questionnaire on UV exposure, any changes in the esthetics of the product, and where it had been stored.

Inclusion Criteria

- Male or female subjects of any race or skin type, 12 years of age or older, willing to use the product on a daily basis for 12 months.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were willing and capable of cooperating to the extent and degree required by the protocol, especially in regards to compliance with the long-term dosing requirements.

Exclusion Criteria

- Subjects with a condition, or in a situation, which in the investigator's or sub-investigator's opinion, may have suggested a significant hazard for the subject, may have

confounded the study results, or may have interfered with the subject's participation in the study.

- Subjects with known sensitivities to any of the study preparations.
- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

Each subject received both verbal and written instructions as to the proper dosing and study drug application techniques. The subjects were directed to apply the study drug to the whole face, neck and hands each morning. This was the minimum surface area that needed to be covered by the sunscreen at least once each day.

Application of the study drug to other parts of the body was possible. The application to other exposed skin areas, in particular the forearms and upper chest, was encouraged, particularly during summer months. The study drug could be used occasionally for sun protection during longer periods of sun exposure; however, other sunscreens (possibly with higher SPFs) could have been utilized for this purpose. The subject was to tell the investigator where the other sunscreens were applied and to record this information in the diary. The subject was to record all products that were used on the face, hands, and neck, including cosmetics or topical drugs.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession and were then assessed by the site personnel for compliance with study drug application. The site personnel assessed the tubes as empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.

Study drug containers were collected and examined by designated site personnel at the 2-, 4-, 6-, 8-, 10- and 12-month study visits to document usage. Subjects were also questioned regarding study drug application technique and frequency of application. Subjects reported the study drug usage on a daily basis in the subject diary. All used tubes were returned following the 6- and 12-month visit and a weight was taken and recorded by the labeler,

Study PEN.750.01: Flow Chart of Study Procedures

	Month							
Procedures	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At the request of the Agency, Protocol PEN.750.01 was extended to 12 months in duration. It was also designed to recruit approximately half of the subjects from sites in geographical locations with high sunlight exposure, such as Scottsdale, Arizona and Modesto and Santa Monica, California. As per the Agency's recommendation, this protocol was designed to incorporate the return and weighing of used product tubes at the conclusion of the study. In addition, a questionnaire was added to the Case Report Form to collect data from the subjects at 2-month intervals regarding product consistency/integrity (texture, color change, and odor) as well as storage conditions and additional questions on sun exposure. This study did not include children from 6 months to 12 years of age since it is unlikely that the product would be used by children under 12 years of age, due to the positioning of the product as a daily-use facial moisturizer cosmetic containing sunscreen.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diary for any information that may have indicated a change in status from baseline or any adverse events. Any time a subject experienced a severe adverse drug experience they were encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

All demographic data, evaluations and other observations were recorded directly, promptly and legibly in black ink on the CRF. Completed CRFs were signed by the investigator. Data from the CRFs were captured in a software package that was customized for data entry and that maintained an electronic audit trail. All data was double entered except for comments.

All study statistics for the primary endpoints were to be descriptive. Approximately 250 subjects were to be enrolled in the study in order to obtain approximately 200 subjects with 12 months of product usage.

10.1.2 **PEN.750.02.** Clinical safety trial of long-term intermittent use of (b) (4) sunscreen (760-006)

The objective of this study was to determine the long-term safety of (b) (4) Sunscreen (760-006) in intermittent long-term use conditions in normal subjects, including children 6 months of age and older.

This was a multicenter, open-label, uncontrolled safety trial of product usage in normal subjects, including children 6 months of age and older.

No particular inclusion or exclusion criteria were applied to subjects to identify them as having sensitive skin. However, it was recorded in the CRF if the subject had self-assessed sensitive skin (i.e., in the subject's opinion), or if he/she had an atopic background (atopic dermatitis, allergic rhinitis or asthma in personal history) or previous intolerance problems to topical products, including cosmetics. The phototype (based on the Fitzpatrick scale 3VI described in the monograph") and the type of skin (oily, normal, dry and combination skin) was recorded at the baseline visit as well.

Inclusion Criteria:

- Male or female subjects of any race or skin type, 6 months of age or older, willing to use the product for 12 months. During the 12-month period, each subject was to plan for at least 14 days with outdoor activities, such as a beach vacation or weekend gardening or sport activities, where the use of a sunscreen was required.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were willing and capable of cooperating to the extent and degree required by the protocol, especially in regards to compliance with the long-term dosing requirements.

Exclusion Criteria:

- Subjects with a condition, or in a situation, which in the investigator's or sub-investigator's opinion, may have suggested a significant hazard for the subject, may have confounded the study results, or may have interfered with the subject's participation in the study.
- Subjects with known sensitivities to any of the study preparations.

- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

A subject could withdraw from the study at any time and for any reason. The reasons stated for withdrawal were documented in detail on the subject's CRF and on the Adverse Event form if need be. Participation in the study could have been discontinued:

- either at the investigator's request, for safety reasons (e.g., severe adverse reactions, or conditions that may have jeopardized the subject's health if they were to continue in the trial), or at the subject's request;
- for deviations or non-compliance with the requirements of the protocol;
- when a subject was lost to follow-up. The investigator was to attempt to reach the subject with two telephone calls and a certified or registered letter before considering the subject lost to follow-up. These actions were to be reported in the comment section of the Exit Form, and a copy of the follow-up letter was to be maintained in the investigator's file.

At the baseline visit, for demonstration purposes, the investigator or designee applied the first dose of study drug. The investigator or designee showed the subject how to use the product and directed the subject to apply wherever the sun could reach the skin during the anticipated sun exposure. Subjects also had written instructions that they could refer to. The study drug was to be applied as homogeneously as possible to all sun-exposed areas. In the case of small children, the parents/guardians applied the study drug. Make-up products such as lipsticks or foundations containing sunscreens were permitted as daily cosmetic products. During the study, the subjects recorded all topically used products that were applied to the area where the study drug was applied. Use of any product that contained sunscreen (make-up, foundation, cream, moisturizer, aftershave, etc.) was to be documented in the concomitant therapy form.

The study drug was to be reapplied, at the discretion of the subject, as needed during extended outdoor usage. The subjects were instructed to re-apply frequently, as needed.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession. At the same time, subjects were also assessed for compliance by the site personnel. The site personnel assessed if the tubes were empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.

Study drug containers were collected and examined by designated site personnel at the 2-, 4-, 6-, 8-, 10-, 12-month study visits to document usage. All remaining materials were collected at the 12-month visit. Subjects were also questioned regarding test-material application technique and frequency of application. Subjects reported the product usage on a daily basis in the subject diary.

The following procedures were performed by designated, trained personnel on the corresponding visit day:

Study PEN.750.02: Flow Chart of Study Procedures

	Month							
Procedures	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At Visit 1 (baseline), the investigator thoroughly examined the skin of each participant to collect information on interfering conditions, signs and symptoms, or skin abnormalities, especially on the areas where the study drug was to be applied. This information was recorded on the appropriate CRF. At each follow-up visit, the investigator examined all areas of the skin to which the subject had applied the study drug, specifically to look for cutaneous signs of irritation, sensitization, or photosensitivity.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diaries for any information that may have indicated a change in status from baseline or any adverse events. Any time subjects experienced a severe adverse drug experience, they were encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

Adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporary associated with the use of a drug.

The investigator assessed the relationship (causality) of an AE to the study drug according to the following definitions:

- Definitely Related. No uncertainty about the relationship between the event and test drug administration. The event follows a definite reasonable temporal sequence from the time of test drug administration and improves upon stopping the dose of the study drug. A re-challenge is positive. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject. The event follows a known response pattern to the study drug.
- Probably related. High degree of certainty about the relationship between the event and test drug administration. The event follows a reasonable temporal sequence from the time of test drug administration and improves upon stopping the dose of the study drug. The event cannot be reasonably explained by the known characteristics of the subject's clinical state or by other modes of therapy administered to the subject.
- Possibly related. Unlikely but cannot rule out with certainty the relationship between the event and test drug administration. The event may follow a reasonable temporal sequence from the time of test drug administration. The event may have been produced by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.
- Unlikely related. Clinical event has an unlikely relationship with the test drug administration. There is no reasonable temporal association between the study drug and the suspected event and the event could have been reasonably produced by the subject's clinical state or other modes of therapy administered to the subject.
- Unrelated. Clinical event is clearly not due to test drug administration. There is no reasonable temporal relationship between the test drug administration and the suspected event (e.g., event occurs before test drug administration) or no reasonable causality, such as in accidents which cannot be remotely related to study participation (injuries sustained in a car accident).

All study statistics for the primary endpoints were descriptive. Adverse drug experiences were described and tabulated. As this trial was open and non-comparative, only descriptive data presentations were made, and no formal statistical hypothesis was tested.

The Safety Population was defined as all subjects enrolled and treated at least once with study drug. The Safety Population was the primary population used for the analyses.

Demographic and baseline characteristics were summarized by descriptive statistics. For the continuous variable, age, the following descriptive statistics were provided: sample size (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For categorical variables, sex, race, and skin phototype, counts and percentages were provided. Subject disposition was tabulated and reasons for discontinuation were summarized by counts and percentages.

Adverse events were coded against a modified COSTART dictionary of terms prior to any analyses and therefore, body systems and preferred terms were available for all AEs. All information pertaining to AEs noted during the study were listed by subject, detailing verbatim given by the investigator, the preferred term, the body system, start/stop dates, severity, and drug relatedness. The AE onset was also shown relative (in number of days) to the day of initial dose of the study drug.

For this study, the planned number of subjects (250) for treatment for up to 12 months at dosage levels intended for clinical use was thought to be adequate to characterize the pattern of AEs over time. The sample size for this study was established from the ICH El Guideline on the Extent of Population Exposure to Assess Clinical Safety." To achieve this objective the cohort of exposed subjects was to be 300-600 subjects for 6 months treatment and 100 subjects for a year. Therefore, this study was designed to enroll 250 subjects, taking into account an anticipated drop out rate of 25%.

10.1.3 **PEN.750.03.** Clinical safety trial of long-term intermittent use of (b) (4) sunscreen (539-106)

The objective of this study was to determine the long-term safety of (b) (4) Sunscreen (539-106) in intermittent use conditions for up to 12 months in healthy subjects, including children 6 months of age and older.

This was a two-center, open label, uncontrolled safety trial of product usage. Eighty healthy subjects including children 6 months of age and older were to be enrolled in the study.

The study population was defined according to the following inclusion/exclusion criteria.
Inclusion Criteria:

- Male or female subjects of any race or skin type, 6 months of age or older, who were willing to use the product for 12 months. During the 12-month period, each subject was to plan for at least 14 days with outdoor activities, such as a beach vacation or weekend gardening or sport activities, where the use of a sunscreen was required.
- Subjects (and/or guardians) who signed an informed consent.
- Subjects (and/or guardians) who were willing and capable of cooperating to the extent and degree required by the protocol, especially regarding compliance with the long-term dosing requirements.

Exclusion Criteria:

- Subjects with a condition, or in a situation, which in the investigator's or sub-investigator's opinion, may have suggested a significant hazard for the subject, may have confounded the study results, or may have interfered with the subject's participation in the study.
- Subjects with known sensitivities to any of the ingredients in the study preparations.

- Subjects who participated in a clinical research study, including consumer product studies, within the last 30 days prior to enrollment.

In addition to these criteria, it was recorded in the CRF if the subject had self-assessed sensitive skin (i.e., in the subject's opinion), and if he/she had an atopic background (atopic dermatitis, allergic rhinitis or asthma in personal history) or previous intolerance to topical products, including cosmetics. The skin phototype (based on the Fitzpatrick scale I-IV) and the type of skin (oily, normal, dry or combination skin) were recorded at the baseline visit as well.

Each subject received both verbal and written instructions as to the proper dosing and study drug application techniques. The subjects were directed to apply the study drug wherever the sun could reach the skin during the anticipated exposure. The study drug was to be applied as homogeneously as possible to all sun-exposed areas. In the case of small children, the parents/guardians applied the study drug. Make-up products such as lipsticks or foundations containing sunscreens were permitted as daily cosmetic products. During the study, the subjects recorded all topically used products that were applied to the area where the study drug was applied. Use of any product that contained sunscreen (make-up, creams, foundation, moisturizer, aftershave, etc.) was documented in the concomitant therapy form.

The study drug was to be reapplied, at the discretion of the subject, as needed during extended outdoor exposure. The subjects were instructed to re-apply as frequently as needed.

During the 12 months of the study, subjects were to plan for a significant sun-exposure period, such as a beach vacation or weekend outdoor activities with at least 14 sun-exposure days minimum, where the use of a sunscreen was required. Subjects were allowed to use the study drug on a daily basis on areas such as the face, neck, hands and forearms. Subjects were given a diary in which they recorded daily product usage and sun exposure.

Subjects received a 2-month supply of the study drug treatment (4 tubes) at each visit except the Month 1 visit. The investigator could dispense more tubes, on an individual basis, if deemed necessary. At each follow-up visit, the subjects returned all containers of the study drug in their possession and were assessed by the site personnel for compliance with the study drug application. The site personnel assessed if the tubes were empty, partially used or unused. At follow-up visits, any unused tubes were returned to the subjects and any used or only partially used tubes were replaced with new, sequentially numbered tubes.
All subjects received (b) (4) Sunscreen (539-106).

Neither the investigator nor subject was blinded in this study.

During the baseline visit, a medical history was obtained on each subject and included any pertinent previous and concomitant medications. These were recorded on the CRF. Any therapy used by the subject was considered concomitant therapy (e.g., aspirin, birth control pills, vitamins, moisturizers, etc.). Use of any sunscreen, including sunscreen in cosmetic products such as foundations or moisturizers, aside from the study drug, was recorded as a concomitant therapy. The use of these products was discouraged but was not considered a protocol deviation.

Non-medicated shampoos and soaps were not recorded in the CRF. Subjects were instructed to notify the investigator if there were any changes in the dosage of any concomitant therapy.

Study drug containers were collected and examined by designated site personnel at the 2, 4, 6, 8, 10, and 12-month study visits to document usage. Subjects were also questioned regarding study drug application technique and frequency of application. Additionally, subjects reported the product usage on a daily basis in the subject diary.

Upon receipt of the clinical supplies, the investigator (or other designated study personnel) conducted a complete inventory of all study drug materials and assumed responsibility for their storage and dispensing. In accordance with regulations, study drug materials were kept in a secure, locked location with restricted access.

The following procedures were performed during the course of the study:

Study PEN.750.03: Flow Chart of Study Procedures

	Month							
Procedures	Baseline Visit 1	1 Visit 2	2 Visit 3	4 Visit 4	6 Visit 5	8 Visit 6	10 Visit 7	12 Visit 8
Informed Consent	X							
Demographics	X							
Inclusion/Exclusion Criteria	X							
Medical History	X							
Dermatological Examination	X	X	X	X	X	X	X	X
Subject's Diary Dispensed	X	X	X	X	X	X	X	
Subject's Diary Collected		X	X	X	X	X	X	X
Questionnaire Completed	X		X	X	X	X	X	X
Medication Dispensed	X		X	X	X	X	X	
Medication Returned			X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X
Urine Pregnancy Test								X
Exit case Report Form								X
Adverse Events		X	X	X	X	X	X	X

If a subject discontinued prematurely, all Month 12 (Visit 8) procedures were to be performed at the subject's final visit.

At Visit 1 (baseline), the investigator thoroughly examined the skin of each subject to collect information on interfering conditions, signs and symptoms, or skin abnormalities, especially on the areas where the study drug was to be applied. This information was recorded on the

appropriate CRF page. At each follow-up visit, the investigator examined all areas of the skin to which the subject had applied the study drug, to specifically look for signs of cutaneous irritation, sensitization, or photosensitivity.

Safety was measured by the occurrence of adverse events. At each visit, the investigator asked the subject an open question regarding their health and medical status since the last visit. The investigator reviewed the subject's diaries for any information that may have indicated a change in status from baseline or any adverse events. If a subject experienced a severe adverse drug experience, he or she was encouraged to come to the site, regardless of whether it was between regularly scheduled visits.

All demographic data, evaluations and other observations were recorded directly, promptly and legibly in black ink on the CRF. The investigator signed the completed CRFs. Any changes in entries were made so as not to obscure the original entry and all changes were dated and signed at the time of the change.

The study was conducted under the sponsorship of L'OREAL USA Products, Inc. in compliance with all appropriate local regulations as well as the International Conference on Harmonization (ICH) Guidelines. At the end of the study, [redacted] conducted an audit of the data, documentation and text portions of this report. b(4)

All study statistics for the primary endpoints were descriptive. Adverse events were described and tabulated. As this trial was open and non-comparative, only descriptive data presentations were made, and no formal statistical hypothesis was tested.

Two independent study centers each were to enroll 40 subjects. Subjects were stratified into the following age groups: 6 months to < 2 years, > 2 years to < 6 years, > 6 years to < 12 years, >12 years to < 18 years, and > 18 years to < 65 years. In accordance with the pediatric rule, subpopulations of ages were selected so that approximately 70% of the subjects would be 12 years of age or younger, and results analyzed for the different age groups.

The safety population was defined as all subjects enrolled and treated at least once with the study drug. The Safety Population was the primary population used for the analyses.

Demographic and baseline characteristics were summarized by descriptive statistics. For the continuous variable, age, the following descriptive statistics were provided: sample size (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For categorical variables, sex, race, and kin phototype, counts and percentages were provided. Patient disposition was tabulated and reasons for discontinuation were summarized by counts and percentages.

Adverse events were coded against a modified COSTART dictionary of terms prior to any analyses and therefore, body systems and preferred terms were available for all AEs. All information pertaining to AEs noted during the study was listed by patient, detailing verbatim given by the investigator, the preferred term, the body system, start/stop dates, severity, action

taken, and drug relatedness. The AE onset was also shown relative (in number of days) to the day of initial dose of the study drug. A subset of subjects was identified from medical histories, baseline examinations and certain nonrelated adverse events who are considered predisposed to dermatologic conditions.

Eighty subjects were enrolled in the study for treatment up to 12 months. This study was designed to enroll 60 subjects with an anticipated drop-out rate of 25%. About 45 subjects were anticipated to complete the study including 15 in the age group of 6 months to 2 years of age and 15 in the age group of 2 to 6 years of age. It was thought that the number expected to complete the study would be adequate to characterize the pattern of AEs over time in these particular age

10.2 Line-by-Line Labeling Review

An interdisciplinary scientist in the ONP is reviewing the proposed labeling for the products.

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