

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-009**

**CHEMISTRY REVIEW(S)**

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Nonprescription Clinical Evaluation  
**NDA:** 22-009  
**Applicant:** L'Oréal USA Products  
**Stamp Date:** May 31, 2007  
**PDUFA Date:** March 31, 2008  
**Trademark:** Various  
**Established Name:** Ecamsule, Avobenzone, Octocrylene, and Titanium Dioxide  
**Dosage Form:** Cream  
**Route of Administration:** Topical  
**Indication:** Prevention of sunburn and skin damage following chronic exposure to ultraviolet radiation

**PAL:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>

**Summary and Critical Issues:**

**A. Summary**

There are four proposed drug substances: ecamsule, avobenzone USP, octocrylene USP, and titanium dioxide USP. The applicant references the following DMFs for the CMC information of three drug substances.

Ecamsule	DMF 15517 held by Chimex (Mournex, France)
Avobenzone	DMF _____ held by _____
Octocrylene	DMF _____ held by _____

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A letter of authorization is provided for each DMF. The DMFs were the same DMFs referenced in sunscreen NDAs 21-471, 21-501, and 21-502. They have been reviewed and deemed adequate to support the aforementioned sunscreen NDAs.

The CMC information for titanium dioxide USP is provided in the NDA. The titanium dioxide drug substance proposed for this NDA is an \_\_\_\_\_ form manufactured by \_\_\_\_\_ using a \_\_\_\_\_ process. The supplier, the process, and the controls are the same as those approved for NDA 21-471.

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The proposed drug product is an \_\_\_\_\_ cream packaged in 50 mL tubes with \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ The formulation contains 3% ecamsule, 2% avobenzone USP, 10% octocrylene USP, and 5% titanium dioxide USP as the active

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ingredients. The formulation excipients are the following: carbomer 940 NF, carbomer copolymer NF type B, cyclomethicone NF, dimethicone NF 200-350 cst, edentate disodium USP, glycerin USP, hydroxypropyl methylcellulose USP, isopropyl palmitate NF, methyl paraben NF, phenoxyethanol Ph.Eur./NF, polyvinylpyrrolidone/eicosene copolymer, propylene glycol USP, Propylene paraben NF, stearic acid NF, stearyl macroglycerides Ph.Eur., stearyl alcohol NF, trolamine NF, purified water USP. Note that the formulation proposed for this NDA is identical to that approved for NDA 21-471 except an increase in the level of ecamsule (from 2% to 3%) and titanium dioxide (from 2% to 5%). This increase is aimed to enhance the protection ability of the proposed product from UVA/UVB irradiation.

The to-be-marketed formulation and commercial scale manufacturing process are the same as those used in Phase 3 clinical trials and registration stability batches. The designated manufacturing site is also the same site for the manufacture of Phase 3 supplies and registration stability batches. The manufacturing process involves \_\_\_\_\_

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Drug product stability data provided in the initial submission to support the proposed expiry period of 36 months at 20-25°C include long term (25°C/60% RH) data of 36 months from three batches in the to-be-marketed container/closure system. Also provided are the accelerated (40°C/75% RH) stability data of 6 months from three batches, and the study results of a free-thaw study and a light stability study. All registration stability batches were at the commercial scale size, \_\_\_\_\_

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#### B. Critical issues for review

Critical review issues have not been identified for this NDA mainly because all critical CMC elements of drug substance and drug product have been reviewed and approved in earlier sunscreen NDAs. Some non-critical deficiencies and differences from earlier NDAs are noticed in this filing review and presented below:

##### Drug Substances

- A new HPLC method is proposed for ecamsule assay and related substances.
- The drug substance specification appears to be slightly different from that approved under NDA 21-471 for ecamsule and avobenzone.
- Post approval commitment for drug substances can not be found in the NDA.

##### Drug Product

- Packaging component information can not be found for the \_\_\_\_\_ size configuration mentioned in Module 2 Quality Summary and Module 3 Stability. This is not a critical issue because the \_\_\_\_\_ size is not proposed for commercialization.
- The drug product specification does not include ecamsule related substances.

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Additionally, the proposed product is the same product proposed for \_\_\_\_\_

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\_\_\_\_\_ It is necessary to review the CMC

deficiencies outlined in the AE letter, and assess if the applicant has addressed them adequately in this NDA.

C. Comments for 74-Day Letter

None

D. Comments/Recommendation:

The application is fileable from the CMC and quality perspective.

Drug substance facilities are located in \_\_\_\_\_ Drug product facility is located in New Jersey, USA. GMP inspection requests have been submitted.

**b(4)**

Shulin Ding  
Pharmaceutical Assessment Lead

Moo Jhong Rhee  
Chief, Branch III

## Filing Checklists

### A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	Non-CTD format
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

### B. Technical Checklists

#### 1. Drug Substance Referenced to DMFs.

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
x		Does the section contain specifications?	
x		Does the section contain information on impurities?	
x		Does the section contain validation data for analytical methods?	
		Does the section contain container and closure information?	Not applicable.
x		Does the section contain stability data?	

#### 2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	The proposed trade name is uncertain.

### C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
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	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/s/

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Shulin Ding  
7/16/2007 05:17:44 PM  
CHEMIST

Moo-Jhong Rhee  
7/17/2007 04:47:10 PM  
CHEMIST  
Chief, Branch III



CMC REVIEW



**NDA 22 009**

**HelioBlock® SX Sunscreen Cream (SPF 40)**

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

Christopher Hough

Review Chemist

**Office of New Drug Quality Assessment  
Division of Office of New Drug Quality Assessment  
Pre-Marketing Division II, Branch III**

CMC REVIEW OF NDA 22-009

**For the Division of Nonprescription Clinical Evaluation  
Office of Non-Prescription Products  
(HFD-560)**



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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 22-009
2. REVIEW #: 1
3. REVIEW DATE: 15-Jan-2008
4. REVIEWER: Christopher Hough

5. PREVIOUS DOCUMENTS:

Document	Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission Correspondence (C)	31-May-2007

7. NAME & ADDRESS OF APPLICANT:

Name: L'Oreal USA Products, Inc  
 Address: 30 L'Oreal Way, Clark, New Jersey 07066  
 Representative: Jean R. Grieve  
 Telephone: 732.680.5562

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: UV Expert/Anthelios/Capital Soleil
- b) Non-Proprietary Name: Combination of Ecamsule 3%, Avobenzone 2%, Octocrylene 10% and Titanium Dioxide 5%.
- c) Code Name/# (ONDQA only): Helioblock® SX Cream SPF 40, formula 760.001
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5 (new formulation)
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: sunscreen



## CMC Review Data Sheet

11. DOSAGE FORM: cream
12. STRENGTH/POTENCY: ecamsule 3%, avobenzone 2%, octocrylene 10%, titanium dioxide 5%.
13. ROUTE OF ADMINISTRATION: topical
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product

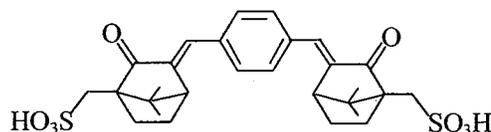
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Ecamsule**

(±)-(3E,3'E)-3,3'-(p-phenylenedimethylidene)bis(2-oxo-10-bornanesulfonic acid)

IUPAC: [(3E)-3-[[4-[(Z)-[7,7-dimethyl-2-oxo-1-(sulfomethyl)-3-bicyclo[2.2.1]heptanylidene]methyl]phenyl]methylidene]-7,7-dimethyl-2-oxo-1-bicyclo[2.2.1]heptanyl]methanesulfonic acid

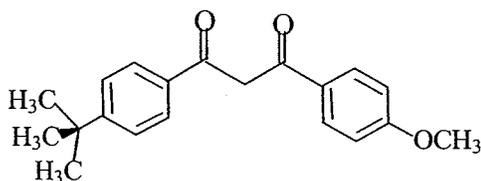
C<sub>28</sub>H<sub>34</sub>O<sub>8</sub>S<sub>2</sub>, MW 562.697, CAS 92761-26-7, also known as Mexoryl<sup>®</sup> SX

**Avobenzone**

1-(p-tert-Butylphenyl)-3-(p-methoxyphenyl)-1,3-propanedione

IUPAC: 1-[4-(1,1-Dimethylethyl)phenyl]-3-(4-methoxyphenyl)-1,3-Propanedione

C<sub>20</sub>H<sub>22</sub>O<sub>3</sub> MW 310.387 CAS 70356-09-1, also known as Avobenzone; Photoplex; Shade uvaguard, Parasol<sup>®</sup> 1789 ...





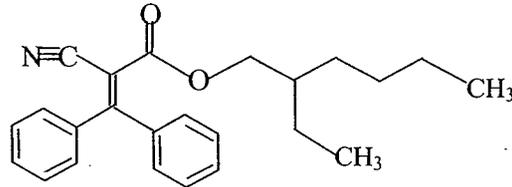
CMC Review Data Sheet

**Octocrylene**

3-Ethylhexyl-2-cyano-3,3'-diphenylacrylate

IUPAC: 2-ethylhexyl 2-cyano-3,3-dicyclohexylprop-2-enoate

C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>, MW: 361.477, CAS 6197-30-4, also known as Octocrylene; UV Absorber-3 ...



**Titanium Dioxide**

TiO<sub>2</sub> MW 79.87 CAS 13463-67-7



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
15517	II	Chimex	Ecamsule	3	Adequate	03-Mar-2006	
					Adequate	03-Mar-2006	
					Adequate	16-Dec-2005	
					Adequate	03-Mar-2006	
					N/A		
					N/A		
					N/A		
					N/A		
					N/A		

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<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,850	This formulation.
IND	59,126	SPF 15 Water Resistant
NDA	21-471	SPF 20 Water Resistant
NDA	21-502	SPF 15 Daily Cream
NDA	21-501	SPF 15 Water Resistant

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18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	22-Jan-2008	OC
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	N/A	N/A	N/A
Methods Validation	Not planned	N/A	N/A
DMETS	N/A	N/A	N/A
EA	N/A	N/A	C. Hough
Microbiology	N/A	N/A	N/A

# The CMC Review for NDA 22-009

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This reviewer recommends approval of this NDA from a CMC perspective.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

### II. Summary of CMC Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### (1) Drug Substance

This application involves four drug substances: Avobenzone, Octocrylene, Ecamsule, and Titanium dioxide. Avobenzone, Octocrylene and Titanium dioxide are generally recognized as being safe and effective and are included in the over-the-counter sunscreen provisions of 21 CFR 352.10, 352.20 and 64 FR27666. Ecamsule has been previously reviewed and approved in NDAs 21-471, 21-501 and 21-502. The Titanium dioxide used in this application is the \_\_\_\_\_

\_\_\_\_\_ Most commonly used as an excipient, this drug substance does not have a DMF for manufacturing information but is deemed acceptable from the CMC perspective solely on the basis of data submitted by the sponsor. The other drug substances refer to their respective DMFs. The recent addition of a revised protocol for the assay of impurities in Ecamsule allowed the sponsor to tighten the acceptance criteria for this drug substance. The application appears to be complete with respect to the drug substance sections and to be satisfactory for use in the drug product.

##### (2) Drug Product

The drug product is a mixture of four drug substances and eighteen excipients. The active ingredients are present as 2% Avobenzone, 10% Octocrylene, 3% Ecamsule, and 5% Titanium dioxide. 21CFR 352.20 stipulates that combinations of up to 3% Avobenzone, 10% Octocrylene and 25% Titanium dioxide are permitted as long as each contributes at least 2 SPF of protection. The addition of Ecamsule occasioned NDA submission. The eighteen excipient mixture produces a formulation that is both stable and flexible. Stability data support an expiration date of at least 3 years from

b(4)

## Executive Summary Section

the date of manufacture. Unfortunately, an Agency request for tightening the acceptance criteria of a related sunscreen product (NDA 21-501) prompted the sponsor to do so for the present application after the stability testing batches of drug product had been released and the stability studies begun. The results of these studies show, however, that the aforementioned stability testing batches meet the narrower specification as well. The sponsor has committed to using the new, narrower specification for drug product in all releases for commercialization and stability tests in the future. A recommendation of "Approval" is forwarded on the basis of this CMC review.

**B. Description of How the Drug Product is Intended to be Used**

The drug product is intended to be applied topically to skin exposed to the sun's rays as necessary to maintain protection against both UV A and UV B radiation. This cream is not resistant to washing with water or perspiration.

**C. Basis for Approvability or Not-Approval Recommendation**

The recommendation of "Approval" for the drug product is made on the basis of sufficient evidence that the identity, purity, strength, and quality of the drug substance and drug product are assured per 21 CFR 314.50 (d)(1).

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Christopher J. Hough, Ph.D., Branch III, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch III, ONDQA

**C. CC Block:** entered electronically in DFS

48 Page(s) Withheld

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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CHEMIST  
Chief, Branch III