CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-129

CHEMISTRY REVIEW(S)

MEMORANDUM

Date: March 24, 2009

To: NDA 22-129

From: Elaine Morefield, Ph.D.
Division Director
Pre-marketing Assessment Division II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 22-129 Trade name (benzyl alcohol), Lotion 5%, by Sciele® Pharma, Inc.

The drug product "Trade name (benzyl alcohol), Lotion 5%", contains (50mg/g) of benzyl alcohol as an active ingredient. It is a non-pesticide pediculocide for the topical treatment of head lice. The drug product is free flowing smooth white lotion. The proposed container/closure system for the drug product is an 8 oz natural (opaque) polypropylene (b) (4) round bottle (b) (4)

I have assessed the ONDQA review of NDA 22-129. I believe that there are adequate manufacturing procedures and controls for production of a quality product. I concur with the approval recommendation from a CMC perspective.

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/s/

Elaine Morefield
3/26/2009 09:41:08 AM
CHEMIST

NDA 22-129

Tradename (benzyl alcohol), Lotion 5%

Sciele® Pharma, Inc.

Tarun Mehta, M.Sc.

Review Chemist

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

CMC REVIEW OF NDA 22-129
Division of Dermatology and Dental Products (HFD-540)

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 22-129

2. REVIEW #: 2

3. REVIEW DATE: 11-Feb-2009

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	Document Date
Original	June 15, 2007
Amendment 0001	July 19, 2007
Amendment 0002	August 31, 2007
Amendment 0005	September 28,2007
Amendment 0012	January 25, 2008
Amendment 0013	February 05, 2008
Amendment 0014	March 04, 2008
Amendment 0015	March 19, 2008
Letter for Dosage Form Change	April 30, 2008 (Dosage form change)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 0021	June 17, 2008 (transfer of ownership)
Amendment 0022	June 30, 2008 (trade name - (b) (4)
Amendment 0027	October 17, 2008 (Label revised)
Amendment 0030	December 30, 2008 (Drug substance container revised)
Amendment 0031	February 10, 2009 (Post approval commitments)

7. NAME & ADDRESS OF THE APPLICANT:

Name:	Sciele® Pharma Inc.
Address:	5 Concourse Parkway Suite 1800, Atlanta, GA 30328
Representative:	Debra Hayes, RAC Regulatory Manager

Chemistry Review Data Sheet

Telephone: 678 – 341 – 1526 ; dhayes@sciele.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename
b) Non-Proprietary Name (USAN): Benzyl Alcohol
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL CATEGORY: Non-pesticide pediculicide

11. DOSAGE FORM: Lotion

12. STRENGTH/POTENCY: 5%

13. ROUTE OF ADMINISTRATION: Topical

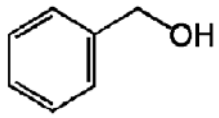
14. Rx/OTC DISPENSED: _x_ Rx __ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

Chemical Name: phenyl methanol



Chemical Structure:
Molecular weight: 108.14
Molecular formula: C_7H_8O

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Benzyl Alcohol NF drug substance	1	Adequate	8/24/07	Reviewed by Tarun Mehta
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	7/16/04	Reviewed by Hsich, Li Shan
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF is not review, 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")

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

18. STATUS:

ONDQA:

CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	November 19, 2008	(b) (4)

Chemistry Assessment Section

The Chemistry Review for NDA 22-129

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug substance

(1) Drug Product

The drug product "Tradename (benzyl alcohol) 5% Lotion" containing 5% (50mg/g) of benzyl alcohol as an active ingredient. Final drug product contains (b) (4) benzyl alcohol, which is (b) (4) The drug product is free flowing smooth white lotion. All the excipients in this formulation are compendial (USP/NF).

In the formulation, (b) (4)

The development and manufacturing of the clinical batches were conducted at Contract Pharmaceutical Limited. The drug product compositions of the clinical batch and the proposed commercial batch are identical. A commercial size (b) (4) batch was successfully manufactured at the proposed scale-up site, using the proposed commercial manufacturing process and equipment. The manufacturing process controls assure the consistent quality of the drug product. The identity, strength, and purity of the drug product are evaluated by the following analytical tests: description, pH, viscosity, specific gravity, benzyl alcohol ID, assay, and related substances. The specification for the drug product is deemed satisfactory.

The proposed container/closure system for the drug product is an 8 oz natural (opaque) polypropylene (b) (4) Information provided for the proposed container/closure is deemed adequate.

Stability data (updated in the amendment 0002; August 31, 2007) derived from the three stability batches packaged in the proposed container/closure met the specification for the drug product stored up to 24 months at 25^0C/60% RH condition. There was no significant trend found in the results. Based on the adequate 24 months stability data, the expiration-dating period of 30 months is granted.

(2) Drug Substance

(b) (4) manufactures the benzyl alcohol. The chemistry, manufacturing, and controls information on the drug substance is provided in DMF (b) (4) which is deemed adequate to support this application.

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

The drug product is indicated for topical treatment of head lice in patients of 6months or older. Tradename (benzyl alcohol) 5% lotion applies once weekly for two weeks. Apply Tradename directly to DRY hair, completely cover the entire scalp and all hair, including the area around the ears and nape of the neck. Allow Tradename to remain in the hair for at least 10 minutes. After 10 minutes, it should be thoroughly rinsed from the hair with water. Treatment must be repeated in one week to eliminate any lice that hatched after the first treatment.

C. Basis for approvable recommendation:

The sponsor has provided sufficient information on raw material controls, manufacturing process and process controls, and adequate specification for assuring consistent product quality of the drug substance and drug product. The NDA has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendation.
All labels have the required information.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

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

Project Manager: Nichelle Rashid

52 pages of b4 (CCI/TS) information has been withheld after this page.

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/s/

Tarun Mehta
2/11/2009 03:53:33 PM
CHEMIST

Moo-Jhong Rhee
2/11/2009 04:14:45 PM
CHEMIST
Chief, Branch III

NDA 22-129

Tradename (benzyl alcohol), Lotion 5%

Summer Laboratories, Inc.

Tarun Mehta, M.Sc.

Review Chemist

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

CMC REVIEW OF NDA 22-129
Division of Dermatology and Dental Products (HFD-540)

Table of Contents

Chemistry Review Data Sheet

1. NDA #: 22-129

2. REVIEW #: 1

3. REVIEW DATE: 15-April-2008

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWS:

Submission(s) Reviewed	Document Date
Original	June 15, 2007
Amendment 0001	July 19, 2007
Amendment 0002	August 31, 2007
Amendment 0005	September 28,2007
Amendment 0012	January 25, 2008
Amendment 0013	February 05, 2008
Amendment 0014	March 04, 2008
Amendment 0015	March 19, 2008
Letter for Dosage Form Change	April 30, 2008

7. NAME & ADDRESS OF THE APPLICANT:

Name:	Summers Laboratories, Inc.
Address:	1030 G.P.Clement Dr. Collegeville, PA 19426
Representative:	Glen Park, Sr. Director, Clinical & Regulatory Affairs
Telephone:	212-681-2100

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename®
b) Non-Proprietary Name (USAN): Benzyl Alcohol
c) Code Name/# (ONDQA only): Lice Asphyxiator (benzyl alcohol), 5% Lotion
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: Standard

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

10. PHARMACOL CATEGORY: Non-pesticide pediculicide

11. DOSAGE FORM: Lotion

12. STRENGTH/POTENCY: 5%

13. ROUTE OF ADMINISTRATION: Topical

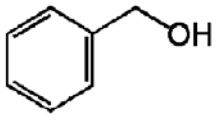
14. Rx/OTC DISPENSED: _x_ Rx __ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x__Not a SPOTS product

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

Chemical Name: phenyl methanol



Chemical Structure:
Molecular weight: 108.14
Molecular formula: C_7H_8O

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Benzyl Alcohol NF drug substance	1	Adequate	8/24/07	Reviewed by Tarun Mehta
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	7/16/04	Reviewed by Hsich, Li Shan

(b) (4)	III	(b) (4)	(b) (4)	3	Adequate		

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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

18. STATUS:

ONDQA:

CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Withhold	March 18, 2008	C. Cruz (301-796-3254)

Chemistry Assessment Section

The Chemistry Review for NDA 22-129

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, the labels do not have adequate information as required. In addition, the drug substance manufacturing facility has not met the cGMP requirements. Therefore, from a CMC perspective, this NDA is recommended for "Approvable" pending resolution of the cGMP issues and label correction.

B. Recommendation on Phase 4 (Post-Marketing) Commitments

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug substance

(1) Drug Product

The drug product "Tradename (benzyl alcohol) 5% Lotion" containing 5% (50mg/g) of benzyl alcohol as an active ingredient. Final drug product contains (b) (4) benzyl alcohol, which is well (b) (4) Appearance of the drug product is free flowing smooth white Lotion.

The drug product contains benzyl alcohol as an active ingredient. Prior to the proposed formulation benzyl alcohol is never been used as an active ingredient in the prescription product. All the excipients and API of this formulation are compendial (USP/NF).

During the formulation, benzyl alcohol is (b) (4)

The drug product development and the clinical supplies manufacturing were conducted at Contract Pharmaceutical Limited. The drug product composition of the clinical supply and the proposed commercial formulation is identical. A commercial size

(b) (4) batch was successfully manufactured at the proposed scale-up site, using the proposed commercial manufacturing process and equipments. The manufacturing process control support the consistent quality of the drug product.
The identity, strength, and purity of the drug product are evaluated by the following analytical tests conducted during the process, on the released finished product and on the stability: Description, pH, viscosity, specific gravity, benzyl alcohol ID, assay, and related substances. The drug product specification is deemed satisfactory.

The proposed container/closure system for the drug product is an 8 oz natural (opaque) polypropylene (b) (4) Information provided for the proposed container/closure is deemed adequate.

Stability results (updated in amendment 0002; august 31, 2007) derived from the three stability batches packaged in the proposed container/closure meet the specification for the drug product stored up to 24 months at 25^0C/60% RH condition. There was no significant trend found in results. Based on the adequate 24 months stability data, the expiration date of 30 months is granted.

(2) Drug Substance

(b) (4). manufactures the benzyl alcohol. The chemistry, manufacturing, and controls information on the drug substance is provided in DMF (b) (4) which is deemed adequate to support this application.

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

The drug product is indicated for topical treatment of head lice in patients of 6months or older. Tradename (benzyl alcohol) 5% lotion applies once weekly for 2 weeks. Apply Tradename directly to DRY hair, completely cover the entire scalp and all hair, including the area around the ears and nape of the neck. Allow Tradename to remain in the hair for at least 10 minutes. After 10 minutes, it should be thoroughly rinsed from the hair with water. Treatment must be repeated in one week to eliminate any lice that hatched after the first treatment.

C. Basis for approvable recommendation:

This NDA provided adequate information on the raw material controls, specification, and container/closure. It also provided sufficient CMC information and stability data to assure identity, strength, purity, and quality of the drug product at the time of release and during the shelf life. However, the labeling required additional information and correction. In addition, the drug substance manufacturing process is not deemed to assure the identity, strength, purity, and quality by lack of cGMP compliance.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Tarun Mehta, M.Sc.

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

Project Manager: Maria Walsh

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/s/

Tarun Mehta
7/3/2008 02:23:42 PM
CHEMIST

Moo-Jhong Rhee
7/3/2008 02:24:48 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	22-129
Applicant:	Summers Laboratories, Inc.
Stamp Date:	June 15, 2007
PDUFA Date	Dec. 15, 2007
Trademark:	(b) (4)
Established Name:	Benzyl Alcohol
Dosage Form:	(b) (4)
Route of Administration:	Topical
Indication:	For patients infected with Pediculus human capitas (head lice) of the scalp hair
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

The proposed drug substance is benzyl alcohol, NF. The applicant references to DMF (b) (4) held by (b) (4) for CMC information of benzyl alcohol. A letter of authorization is provided. The DMF has never been reviewed. The applicant also provides in the NDA the following drug substance information: regulatory specification, method validation, batch analysis, impurities, and stability.

The proposed drug product, (b) (4) (benzyl alcohol) (b) (4) 5%, is an (b) (4) packaged in unit-of-use, 8 fl. ounce, (b) (4) polypropylene bottles. The formulation contains 5 % benzyl alcohol as the active ingredient and the following excipients: carbomer 934P, NF; mineral oil, NF; polysorbate 80, NF; sorbitan monooleate, NF; trolamine, NF; purified water, USP. The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches.

The manufacturing process and the designated manufacturing site are the same as that used for the manufacture of Phase 3 supplies and registration stability batches. The manufacturing process consists of the following steps: (b) (4)

Drug product stability data provided in the initial submission to support the proposed expiry period of 30 months at controlled room temperature of 25°C with excursions permitted to 59-

86°F (15-30°C) include long term (25°C/60% RH) data of 18-24 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 photostability study. All registration stability batches were (b) (4) which is (b) (4) of the proposed commercial scale (b) (4)

B. Critical issues for review

Environmental Assessment

- The applicant claims categorical exclusion on the basis of no increase in the use of the proposed drug substance (21 CFR 25.31(a)). No information is provided to support the claim. Neither was the concentration of benzyl alcohol at the point of entry into the aquatic environment provided. In order for the Agency to assess the requested categorical exclusion from the preparation of an Environment Assessment, the sponsor must provide production forecast for 5 years and calculate the concentration of benzyl alcohol at the point of entry into the aquatic environment.

Trade name and labels

- There is inadequate information for label/labeling review. Specifically, the proposed trade name for the product is not clearly stated in the NDA, and trade dressing for labels is not provided.

Dosage Form Nomenclature

- The applicant proposes (b) (4) as the dosage form. According to CDER Data Standards Manual, (b) (4) is used as a dosage form term unless a more specific term is applicable, e.g. cream, lotion, and ointment. A sample received before the ND submission indicates that the proposed product behaves like a lotion. Lotion, however, is generally for external application to the skin. Therefore, the term "lotion" may not be appropriate for this product, which is for application to hair and scalp. To assist the assessment of dosage form nomenclature and confirm the product's conformance to lotion definition, the applicant should officially submit a representative sample to the NDA with rheograms.

Registration Stability Batch size

- All three drug product registration stability batches are smaller than (b) (4) of the proposed commercial batch size.

Extractables

- The applicant indicates the detection of extractables in a study required by USP<661>. The applicant, however, did not include extractables in the drug product stability studies. Therefore, it is uncertain whether there are extractables in the proposed product. If there are, the applicant must provide information regarding identity and quantitation.

Drug Substance Stability

- The applicant provides only one month of accelerated stability data from 3 batches stored under ICH conditions to support a retest date of (b) months. Long term stability data generated under ICH storage conditions are not provided. The

absence of long term data generated from ICH conditions renders specification setting difficult, if not impossible. To support drug substance stability, the applicant also provides 24 month stability data from two batches stored under ambient conditions.

C. Comments for 74-Day Letter

Request the applicant to provide the following information to facilitate the review:

- Production forecast for 5 years and the concentration of benzyl alcohol at the point of entry into the aquatic environment
- Proposed trade name for the product, and samples of labels with proposed trade dressing
- Updated stability tables for drug product and drug substance
- Representative drug product samples (b) (4) to be shared with medical reviewer)
- Rheograms (viscosity versus shear rate and shear stress versus shear rate) of the formulation

D. Comments/Recommendation:

The application is fileable from the CMC and quality perspective.

The major filing issue is the absence of environmental assessment. However, this issue has been resolved by the applicant's submission (amendment dated July 19, 2007) of estimated concentration of benzyl alcohol at the point of entry into the aquatic environment based on 5 year production forecast. The expected introduction concentration (EIC) is projected to be (b) (4), which is below the categorical exclusion concentration of 1 ppb.

The major review issues of this NDA include the absence of trade dressing, dosage form nomenclature, registration stability batch size, extractables, and drug substance stability.

Drug product facilities are located in Canada. GMP inspection requests have been submitted.

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?	
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 DMF (b) (4).

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
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?	Absence of ICH long term 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?	Trade dressing is not provided.
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?	**The requested drug product specification on benzene is not provided.***
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

*Benzene level in the drug product is no longer a concern because the applicant has proposed in the NDA a control on benzene for **(b) (4)** carbomer 934P raw material, and the proposed limits are acceptable.

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/s/

Shulin Ding
7/26/2007 03:10:09 PM
CHEMIST

Moo-Jhong Rhee
7/26/2007 05:45:57 PM
CHEMIST
Chief, Branch III