CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-524

CHEMISTRY REVIEW(S)

NDA 21-524

Chlorascrub™ Swab [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
***equivalent to 167 mg of Chlorhexidine Gluconate per pouch**

Chlorascrub™ Swabstick [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
***equivalent to 268 mg of Chlorhexidine Gluconate per pouch**

Chlorascrub™ Maxi Swabstick [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
***equivalent to 855 mg of Chlorhexidine Gluconate per pouch**

Les Entreprises SoluMed Inc.

Milton J. Sloan, Ph. D.
Division of Anti-Infective Drug Products, HFD-520

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 5

The Executive Summary 9

I. Recommendations 9

A. Recommendation and Conclusion on Approvability 9

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 9

II. Summary of Chemistry Assessments 9

A. Description of the Drug Product(s) and Drug Substance(s) 9

B. Description of How the Drug Product is Intended to be Used 11

C. Basis for Approvability or Not-Approval Recommendation 12

III. Administrative 12

A. Reviewer's Signature 12

B. Endorsement Block 12

C. CC Block 11

Chemistry Assessment 13

I. DRUG SUBSTANCE 13

1. Description & Characterization 13

a. Description 13

b. Characterization / Proof Of Structure 13

2. Manufacturer 13

3. Synthesis / Method Of Manufacture 14

a. Starting Materials - Specs & Tests 14

b. Solvents, Reagents, etc. 15

c. Flow Chart 15
d. Detailed Description 15
4. Process Controls 15
a. Reaction Completion / Other In-Process Tests 15
b. Intermediate Specs & Tests 15
5. Reference Standard 15
a. Preparation 15
b. Specifications 15
6. Regulatory Specifications / Analytical Methods 15
a. Drug Substance Specifications & Tests 15
b. Purity Profile 16
c. Microbiology 16
7. Container/Closure System For Drug Substance Storage 16
8. Drug Substance Stability 16
II. DRUG PRODUCT 17
1. Components/Composition 17
2. Specifications & Methods For Drug Product Ingredients 23
a. Active Ingredient(s) 23
b. Inactive Ingredients 24
3. Manufacturer 24
4. Methods Of Manufacturing And Packaging 25
a. Production Operations 25
b. In-Process Controls & Tests 30
c. Reprocessing Operations 30
5. Regulatory Specifications And Methods For Drug Product 30
a. Sampling Procedures 30
b. Regulatory Specifications And Methods 30
6. Container/Closure System 35
7. Microbiology 43
8. Drug Product Stability 43
III. INVESTIGATIONAL FORMULATIONS 48

IV. ENVIRONMENTAL ASSESSMENT 50

V. METHODS VALIDATION 51

VI. LABELING 51

VII. ESTABLISHMENT INSPECTION 52

VIII. DRAFT DEFICIENCY LETTER 52

Chemistry Review Data Sheet

1. NDA 21-524

2. REVIEW #: 1

3. REVIEW DATE: December 1, 2004

4. REVIEWER: Milton J. Sloan, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 59,446	December 8, 1999
IND 59,446 N-001 (GC)	March 8, 2000
IND 59,446 N-002 (IM)	July 7, 2000
IND 59,446 N-003 (IC)	August 1, 2000
IND 59,446 N-004 (GC)	October 31, 2000
IND 59,446 N-005 (GC)	November 21, 2000
IND 59,446 N-014 (GC)	April 4, 2002
IND 59,446 N-015 (IC)	April 23, 2002
IND 59,446 N-016 (MR)	April 26, 2002
IND 59,446 N-017 (MR)	May 01, 2002
IND 59,446 N-018 (IM)	May 22, 2002
IND 59,446 N-020(GC)	July 01, 2002
IND 59,446 N-021 (GC)	July 08, 2002
IND 59,446 N-023 (GC)	August 13, 2002
IND 59,446 N-025 (IC)	October 7, 2002
IND 59,446 N-026 (IC)	October 25, 2002
IND 59,446 N-027 (IC)	March 18, 2003
IND 59,446 N-028 (IC)	March 21, 2003
IND 59,446 N-029 (IC)	March 24, 2003
IND 59,446 N-030 (IC)	April 17, 2003
IND 59,446 N-033 (IC)	July 8,, 2003
IND 59,446 N-034 (IC)	July 22, 2003
IND 59,446 N-038 (IC)	October 27, 2003
IND 59,446 N-040 (US)	April 9, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (CMC Pre-Submission)	May 28, 2004
Original (Amendment)	July 26, 2004
Amendment (BZ)	November 10, 2004
Amendment (BC)	February 10, 2005
Amendment (BC)	April 15, 2005
Amendment (faxed)	June 1, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Les Entreprises SoluMed Inc.
Address:	2109 Le Chatelier, Laval (Quebec) Canada H7T 5B3
Representative:	Anna Mallozzi, Regulatory Affairs
Telephone:	(450) 682-6669

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Chlorascrub ™
b) Non-Proprietary Name (USAN): Chlorhexidine Gluconate (3.15%) and Isopropyl Alcohol (70%)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3S
- Submission Priority: Standard Review

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

10. PHARMACOL. CATEGORY: Antiseptic

11. DOSAGE FORM: Swab

12. STRENGTH/POTENCY: 3.15% CHG with 70% IPA

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: ___Rx _X__OTC

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

Chemistry Review Data Sheet

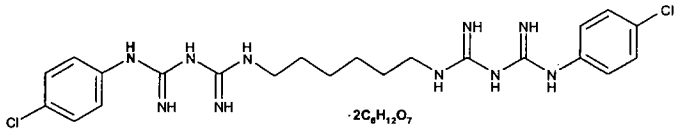
___X___Not a SPOTS product

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

1,1'-Hexamethylenebis [5-(4-chlorophenyl) biguanide] di-D-gluconate

MF: $C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$, MW: 897.8

CAS # 18472-51-0



Isopropanol, 2-propanol

MF: C_3H_8O MW: 60

$(CH_3)_2CHOH$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	CHG, one of the two drug substance	3	Adequate	N/A	None
[redacted]	III	[redacted]	[redacted] aluminum foil	4	Current	N/A	None

[1] 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")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	April 26, 2005	J.D. Ambrogio
Pharm/Tox	N/A	N/A	N/A
Biopharm	N/A	N/A	N/A
LNC	Acceptable with Recommendations; See Labeling Section	5/13/05	Guiragos Poochikian, PhD.
Methods Validation	N/A	N/A	N/A
DMETS	Tradename Review Consult	May 04, 2005	Charlie Hoppes, RPh. MPH
EA	Categorical Exclusion Claimed- Acceptable		Milton J. Sloan, PhD.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-524

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval (AP) from the Chemistry, Manufacturing, and Controls perspective.

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

N/A

II. Summary of Chemistry Assessments

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

Drug Substance

The finished drug products contain two drug substances (chlorhexidine gluconate and isopropyl alcohol) that are described below.

Chlorhexidine gluconate

Chlorhexidine gluconate solution is a colorless to pale yellow aqueous solution of 19.0 to 21.0 percent. The established name is 20% chlorhexidine gluconate solution. Its chemical name is N,N''-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide. It is miscible with water, soluble in ethanol & acetone with a pH: 5.5-7.0. The drug substance is the subject of a USP monograph and has been adequately characterized. Information pertaining to the manufacturing, process controls, specifications, analytical methods, container/closure system and stability has been filed by [redacted] in DMF [redacted] A copy of the letter of authorization (LOA) permitting Les Entreprises SoluMed Inc (SoluMed) to reference the DMF has been included in the NDA. SoluMed proposes the use of the [redacted] standard for CHG. FDA stated in a correspondence (6/1/2001, page 4 and 5 response to question #1and # 6b in Vol. 1.2 of the NDA submission) that the "the test methods and specifications should meet or exceed standards in the USP...". Further reference is made by the sponsor to a telephone conversation (11/08/02) regarding the availability and use of the USP reference standard chlorhexidine diacetate. The USP monograph was not finalized at the time of the IND development studies (see Attachment 3 of Review). The differences in the [redacted] and USP are not expected to be significant in terms of quality rather the analytical methods are the main difference. [redacted] HPLC method is used for USP. [redacted]

that are not part of the USP monograph. The critical parameters (impurity and related substances) for safety are quite similar if not the same. Although the quality of 20% CHG that and USP may be the same, the sponsor has agreed to conform to the official monograph in the USP compendium for commercial marketing of the drug products in the U.S..

Isopropyl alcohol

Isopropyl alcohol (IPA), is an active drug substance that also is an antimicrobial agent. Its chemical name is 2-propanol or propan-2-ol. IPA is a clear, colorless liquid that is miscible with water and has a boiling point of 82.4°C. The drug substance is the subject of USP monograph and has been well characterized. SoluMed initially reported that was the manufacturer and supplier to Nice-Pak (the contract manufacturer of the finished drug products). The sponsor eventually amended the application to declare as the supplier to Nice-Pak facility. See Drug Product section.

Drug Product

SoluMed, has submitted this NDA for three new topical antiseptic/antimicrobial swab drug product presentations for approval to market in the U.S.. The non-sterile finished drug products, Chloroscrub™ Swab, Chloroscrub™ Swabstick, and Chloroscrub™ Maxi Swabstick are formulated to contain a 3.15% (w/v) chlorhexidine gluconate (CHG) solution with 70% (v/v) Isopropyl alcohol and are recommended as:

Chlorascrub™ Swab [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
*equivalent to 167 mg of Chlorhexidine Gluconate per pouch

Chlorascrub™ Swabstick [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
*equivalent to 268 mg of Chlorhexidine Gluconate per pouch

Chlorascrub™ Maxi Swabstick [Chlorhexidine gluconate (3.15%)* and Isopropyl Alcohol (70%) Swab]
*equivalent to 855 mg of Chlorhexidine Gluconate per pouch

Nice-Pak Products Inc. (PDI) will manufacture the bulk solution and package the three drug products. A packager is used to fill the drug product solution and non-sterile swabstick (swab) into a foil pouch and sealed. A summary of the quantitative formula for each of the three drug product presentations are given in Table 1 below. There were several discussions, correspondences with SoluMed during the IND review period on the Chlorascrub™ Swab presentation. SoluMed was asked to show justification on the overage sought for the swab. Because of the study reports that concluded a small amount of CHG was adsorbed onto the material , an overage of was found acceptable and

considered a manufacturing loss. The [redacted] swab contains a preservative [redacted] that has not been adequately studied to show that there is no adverse effect of adsorption of CHG on [redacted] swab. The sponsor has committed to monitor and report the effects of the preservative on chlorhexidine gluconate with the intent to minimize the CHG drug substance overage. Previously, as part of the justification of overage, the request was made for studies to improve the analytical methods to determine the fate of the adsorbed CHG. SoluMed has updated (6/01/05) the NDA with a study to indicate the adsorbed CHG is not undergoing degradation.

Table 1: Summary of Drug Product Presentations

Drug Product	%Label Claim	CHG Quantity/Pouch	IPA Quantity/Pouch	Total Volume/Pouch
Chlorascrub ™ Swabstick	3.15% w/v CHG 70% v/v IPA	268.38 mg	0.88 g	1.6 mL
Chlorascrub ™ Maxi Swabstick	3.15% w/v CHG 70% v/v IPA	855.46 mg	2.8 g	5.1 mL
Chlorascrub ™ Swab	3.15% w/v CHG* 70% v/v IPA	167 mg	0.55 g	1.0 mL

* Calculated based on [redacted] overage [redacted]
The overage for the swab is considered a loss therefore not available and labeled as 3.15% (equivalent to 167 mg of CHG per pouch).

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

Chlorascrub™ Swab is intended for use as a topical antiseptic for preparation of the skin prior to injection [redacted]. Chlorascrub™ Swabstick and Chlorascrub™ Maxi Swabstick are intended for use as a topical antiseptic for preparation of the skin prior to injection [redacted] and intended for use as a patient preoperative skin preparation topical antiseptic for preparation of the skin prior to surgery.

Chlorascrub™ Swab is a [redacted] swab packaged in a [redacted] aluminum foil pouch that contains 1.0 mL of 3.15% CHG and 70% IPA equivalent to 167 mg of CHG per pouch. The drug product is applied over a 2.5 x 2.5 inch treatment area for approximately 30 seconds and dried for 30 seconds.

Chlorascrub™ Swabstick is a 4 ¾ -inch [redacted] stick with a [redacted] foam attached at the tip in [redacted] aluminum foil pouch that contains 1.6 mL of 3.15% CHG and 70% IPA equivalent to 268 mg of CHG per pouch. The tip of the [redacted] The drug product is applied over a 3 x 5 inch (moist or 4 x 4 inch (dry) treatment area for approximately 1.5 minutes and dried for 1.5 minutes.

Chlorascrub™ Maxi Swabstick is a 6-inch [redacted] stick with a [redacted] foam attached at the tip in [redacted] aluminum foil pouch that contains 5.1 mL of 3.15% CHG and 70% IPA equivalent to 855 mg of CHG per pouch. The tip of the [redacted] The drug product is applied over a 3 x 7.5 inch (moist) or 7 x 7 inch (dry) treatment area for approximately 2 minutes and dried for 2 minutes.

C. Basis for Approvability or Not-Approval Recommendation

Chloroscrub™ Swab, Chloroscrub™ Swabstick, and Chloroscrub™ Maxi Swabstick are combination over-the-counter, topical antimicrobial drug product as defined by the TFM (Tentative Final Monograph for Health-Care Antiseptic Drug Products). This 505(b)(2) application relies on the Agency's previous finding of safety for ChloraPrep® (NDA 20-832) a topical antiseptic product containing 2% (w/v) CHG and 70% (v/v) IPA. Les Enterprises SoluMed Inc has a license agreement with Nice-Pak Products Inc. (PDI) to manufacture the bulk solution and package the three drug products. The three drug products have been classified as the same "swab" dosage form and submitted in one NDA. The revised CDER DSM (Data Standards Manual) definition of the swab dosage form is consistent with these proposed drug products. Although the recommendation of DMETS was for a "topical solution" dosage form, Les Enterprises SoluMed Inc. has not proposed to market the bulk solution separately. Internal agreement on the dosage form and nomenclature has been obtained from Labeling and Nomenclature Committee (LNC), as well as Office (ONDC) and Division (DNDCIII) concurrence.

The applicant has satisfactorily demonstrated via the CMC data submitted in the application adequate controls that will assure for this new formulation the identity, strength, quality and purity of the product throughout the recommended shelf life of 24 months. The manufacturing sites have all been found acceptable with the Office of Compliance(see Attachment 1 of Review).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Milton J. Sloan, Ph. D., Chem Reviewer — Date: May 25, 2005
James D. Vidra, Ph. D., Chem TeamLeader — Date: May 27, 2005

CC Block

HFD-520/Archival
HFD-520/DillonParker/PM
HFD-520/Bostwick/MO
HFD-520/Sloan/CHM
HFD-520/Vidra/CHMTL
HFD-830/Schmuff/ActingDivDir
HFD-520/Ellis/PCL
HFD-520/Mahon/MIC
HFD-520/Bell/STT
HFD-560/Frazier/PM
HFD-560/Lumpkins/IDS

50 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Milton Sloan
6/1/05 03:36:57 PM
CHEMIST

Jim Vidra
6/1/05 04:35:46 PM
CHEMIST