Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 13, 2009
To:	Susan Walker, MD, Director Division of Dermatology and Dental Products
Thru:	Kristina C. Arnwine, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Benzyl Alcohol Lotion 5%
Application Type/Number:	NDA 22-129
Applicant:	Sciele Pharma, Inc.
OSE RCM #:	2008-850 and 2008-934

Contents

EXECUTIVE SUMMARY 3
1 BACKGROUND 3
1.1 Introduction 3
1.2 Regulatory History 3
1.3 Product Information 3
2 METHODS AND MATERIALS 4
2.1 Label, Labeling, and Packaging Risk Assessment 4
3 RESULTS 5
4 DISCUSSION 5
5 CONCLUSIONS 5
APPENDICES 6
RESULTS 8

EXECUTIVE SUMMARY

Our analysis of the proposed labels and labeling identified areas of needed improvement. Specifically, we noted inconsistencies in the location and/or presentation of information such as the route of administration and the "Usage Guideline" chart.

We discussed our concerns with the Division of Dermatology and Dental Products (DDDP) review team on February 24, 2009. The review team concurred with our findings and as such our recommendations were forwarded to the Applicant on February 27, 2009.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Dermatology and Dental Products for assessment of the revised container label, carton and insert labeling for Benzyl Alcohol Lotion 5%. Additionally, the Division has requested an assessment of the risk for medication errors with respect to the proposed product container design changes proposed by the Applicant.

1.2 REGULATORY HISTORY

The applicant initially submitted the proposed names (b) (4) and (b) (4) for review and comment. However, the Division of Drug Marketing, Advertising, and Communications (DDMAC) objected to the use of those names from a promotional perspective. DDMAC noted that the names overstate the efficacy of the drug product (see OSE Review 2007-1995 and 2007-1996, dated October 18, 2007) and the Division concurred in an email sent October 15, 2007. Thus, the Applicant submitted the names (b) (4) (primary name) and (b) (4) (alternate name) for review and comment. However, those names were withdrawn by the Applicant on March 28, 2008. Subsequently, the Applicant submitted the names (b) (4) (primary) and (b) (4) (alternate) for review and comment. In OSE Review 2008-463, dated July 3, 2008, we objected to the name (b) (4) due to look-alike similarities with (b) (4) . In OSE Review 2008-464, dated August 21, 2008, we objected to the name (b) (4) due to orthographic similarities to (b) (4) and orthographic and phonetic similarities to (b) (4) a recently approved (June 23, 2008) product. Subsequently, the name (b) (4) was submitted for our review and comment on July 8, 2008 just prior to an approvable action taken on the application on July 14, 2008. The proposed proprietary name, (b) (4) was reviewed under separate cover (OSE Review 2008-1127) and DMEPA initially had no objections to the name. However, the Division stated concern that the name "may lead to medication errors - oral ingestion" and upon further consideration, DMEPA agreed. Thus, the alternate name, (b) (4) was evaluated in OSE Review 2008-1128.

DMEPA addressed the proposed product container design changes in OSE Review 2007-1995/ 2007-1999, dated December 21, 2007. Please refer to that review for our assessment of the container design.

1.3 PRODUCT INFORMATION

Benzyl Alcohol Lotion 5% is indicated for the topical treatment of head lice infestation in patients 6 months of age and older. The product is to be applied directly to dry hair, left on for 10 minutes after application is completed, then rinsed from the hair with water. A fine-tooth comb or special nit comb is helpful to remove dead lice and nits. Treatment must be repeated in one week to completely eliminate any lice that hatched after the first treatment. The amount of product required for treatment depends on the hair length of the person being treated. Benzyl Alcohol will be available in 8 ounce bottles.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff conducting a label, labeling, and packaging risk assessment (see 2.1 Label, Labeling, and Packaging Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL, LABELING, AND PACKAGING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the Division of Medication Error Prevention and Analysis staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention and Analysis reviewed the following revised labels and labeling submitted by the Applicant on October 17, 2008. See Appendix A for pictures of the labels and labeling.

- Container Label
- Carton Labeling
- Insert Labeling (no image)
- “Directions for Use” Sheet

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

See Appendix B for the deficiencies noted following our Label, Labeling, and Packaging Risk Assessment of the labels and labeling submitted by the Applicant on October 17, 2008.

4 DISCUSSION

DMEPA met with the Division of Dermatology and Dental Products (DDDP) review team on February 24, 2009 to discuss the deficiencies we noted in our review of the labels and labeling. A consensus on the proposed recommendations was reached at the meeting. DMEPA's label and labeling comments were forwarded to the Applicant on February 27, 2009.

5 CONCLUSIONS

Our Label, Labeling, and Packaging Risk Assessment identified areas of needed improvements. These label and labeling deficiencies were forwarded to the Applicant on February 27, 2009.

We would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

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Appendix B:

DMEPA's deficiencies noted following our Label, Labeling, and Packaging Risk Assessment of the Labels and Labeling Submitted by the Applicant on October 17, 2008

RESULTS

A. LABEL, LABELING, AND PACKAGING RISK ASSESSMENT

DMEPA requested a working sample of the proposed product container, however, it has not been provided at this time.

B. Packaging

The bottle cap does not contain a child-resistant closure.

C. Container Label and Carton Labeling

The "Dosage and Administration" instructions for use are incomplete when compared to the "Dosage and Administration" section of the insert labeling.

D. Container Label

The route of administration is located on the side panel of the label.

E. Carton Labeling

The "Usage Guideline" chart located in the insert labeling is not located on the carton but would be useful to have in this location also.

F. Insert Labeling

Section 10, *Overdosage*, does not state to seek medical advice "immediately" if oral ingestion occurs.

G. "Directions For Use" Sheet

1. The introductory sentence describes the product as a "special" formulation.
2. The "Usage Guideline" chart in the "Directions For Use" sheet is not identical to the corresponding charts in "Highlights" and Section 17 of the insert labeling.
3. The "Warnings and Precautions" section does not instruct the user on what to do if skin irritation persists after the product has been rinsed with water.
4. There is no information concerning the steps to be taken if the product is orally ingested by accident.
5. There is no information that states whether or not gloves can or should be used with this product.
6. The instructions for use are written for self-application of the product, however, the illustrations show someone else applying the product.
7. Step 2 states to apply the lotion to the "area behind your ears" and "back of your neck". The illustrations that show these steps have these areas of the head circled but because the circles

are over the ear and neck, it is not clear if the lotion is to be applied to the skin or the hair in these areas.

8. Step 4 states to rinse the lotion “from your hair and scalp” but does not specifically state that the hair must be rinsed “with water”.
9. The photograph that is next to the heading “Correct application of TRADENAME Lotion” shows a person with what appears to be hair clips holding the hair in place.

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/s/

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Date:	December 21, 2007
To:	Susan Walker, MD, Director Division of Dermatology and Dental Products, HFD-540
Thru:	Linda Y. Kim-Jung, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, R.Ph., Director Division of Medication Errors and Technical Support, HFD-420
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Errors and Technical Support, HFD-420
Subject:	Medication Error Review
Drug Name(s):	(b) (4) (Benzyl Alcohol) (b) (4) 5%
Application Type/Number:	NDA 22-129
Applicant/sponsor:	Summers Laboratories, Inc.
OSE RCM #:	2007-1995 and 2007-1999

CONTENTS

1 BACKGROUND 1
1.1 Introduction 1
1.2 Regulatory History 1
1.3 Product Information 1
2 METHODS AND MATERIALS 1
2.1 Drug Facts and Comparisons 1
2.2 Clinical Pharmacology Online 2
2.3 AERS Selection of Cases 2
2.4 Expert Panel Discussion (EPD) 3
2.5 Proposed Labeling 3
3 RESULTS 3
3.1 Drug Facts and Comparisons 3
3.2 Clinical Pharmacology Online 4
3.3 AERS 4
3.4 EPD 4
3.5 Proposed Labeling 5
4 DISCUSSION 5
4.1 Dosage Form 5
4.2 Safety Concerns with Product Labels and Packaging 6
5 CONCLUSIONS AND RECOMMENDATIONS 7
5.1 Container Label and Carton Labeling 8
5.2 Insert Labeling 8
6 REFERENCES 9
7 APPENDICES 10
7.1 Drug Facts and Comparisons 10
7.2 Clinical Pharmacology Online 14
7.3 Product Pictures (Taken from Clinical Pharmacology Online and PDR Electronic Library) 20

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Dermatology and Dental Products (HFD-540), regarding the use of the dosage form "lotion" versus "(b) (4) for NDA 22-129, a benzyl alcohol 5% topical product which is to be applied to the **hair** and **scalp** to treat head lice.

The Division informed DMETS that the product is a "lotion" dosage form and were concerned that the term "lotion" may infer the product could be applied all over the body versus just the scalp. The Division requested DMETS input into which term (lotion or (b) (4)) would be safer to use. Additionally, since this question was submitted, labels and labeling were provided to DMETS for review and comment.

1.2 REGULATORY HISTORY

The proposed tradenames for this product ((b) (4) and (b) (4) were not reviewed by DMETS because the Division of Drug Marketing, Advertising, and Comunication (DDMAC) objected to the use of those proposed tradenames and the Division concurred (see OSE Review 2007-1995/2007-1996, submitted on October 18, 2007).

1.3 PRODUCT INFORMATION

(b) (4) (b) (4) (benzyl alcohol) is indicated for patients infected with *Pediculus humanus capitas* (head lice) of the scalp hair. It is to be applied directly to dry hair, left on for 10 minutes after application is completed, then rinsed from the hair with water. A fine-tooth comb or special nit comb is helpful to remove dead lice and nits. Treatment must be repeated in one week to completely eliminate any lice that hatched after the first treatment. (b) (4) will be available in bottles containing 8 ounces.

2 METHODS AND MATERIALS

Since (b) (4) is to be applied only to the hair and scalp for the treatment of head lice, DMETS implemented a search strategy that would enable us to determine if there are any safety issues surrounding the dosage forms "lotion" and (b) (4)" that relate to the use of a product on the hair/scalp. Our initial goal was to identify products that mirror the characteristics of (b) (4) as closely as possible. Once products were identified, we conducted a search of the *Adverse Event Reporting System* (AERS) database for medication errors involving those individual products, specifically medication errors in which the product was applied to areas of the body other than the hair or scalp due to confusion caused by the dosage form designation.

DMETS used the following search strategy to identify products:

2.1 DRUG FACTS AND COMPARISONS

Drug Facts and Comparisons (printed version) was chosen due to the layout and ease of finding the information desired and the dermatology section was searched because of the ease of finding lotions/(b) (4) that would have an indication for use on the scalp and/or the treatment of head lice (see Appendices, Section 8.1). The dermatology section of Drug Facts and Comparisons (printed version) was searched for products that are available in a lotion or (b) (4) dosage form. Once the lotions/(b) (4) were identified, the indications were checked in order to narrow down

the search to products that are either lotions or (b) (4) and are indicated for use on the hair/scalp and/or have an indication for the treatment of head lice.

First search: DMETS searched the dermatology section of Drug Facts and Comparisons for all products that are lotions or (b) (4)

Second search: This search took the results of the first search and looked for products indicated for use on the hair/scalp and/or indicated for the treatment of head lice. The following products were identified as a result of this search: Selenium sulfide 2.5% lotion, malathion lotion, lindane lotion and permethrin lotion. Although lindane lotion is indicated for the treatment of scabies, DMETS included lindane in the search results because it was previously available in multiple dosage forms (lotion, shampoo, and cream) and so a subsequent search for medication errors involving administration of these products might prove helpful in detecting such errors.

2.2 CLINICAL PHARMACOLOGY ONLINE

Clinical Pharmacology Online was searched for all products containing the word "lotion" or "(b) (4) as a dosage form (see Appendices, Section 8.2). This online drug information source was selected because it allows one to search for products based on the dosage form.

First search: DMETS searched Clinical Pharmacology Online for all products that are lotions or (b) (4)

Second search: This search took the results of the first search and looked for products indicated for use on the hair/scalp and/or indicated for the treatment of head lice. The following products were identified as a result of this search: Ala Scalp 2% lotion, betamethasone dipropionate (augmented) 0.05% lotion, amcinonide 0.1% lotion, and betamethasone valerate 0.1% lotion.

2.3 AERS SELECTION OF CASES

We conducted an AERS search on the eight product names identified from Drug Facts and Comparisons and Clinical Pharmacology Online for any medication error cases.

2.3.1 Selenium sulfide

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "selenium sulfide" and tradename "Selsun". The AERS database was searched for cases received through October 3, 2007.

2.3.2 Malathion

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "malathion" and tradename "Ovide". The AERS database was searched for cases received through October 3, 2007.

2.3.3 Permethrin

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", and the active ingredient "permethrin". The AERS database was searched for cases received through October 3, 2007.

2.3.4 Ala Scalp

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", and the tradename "Ala Scalp". The AERS database was searched for cases received through November 21, 2007.

2.3.5 Betamethasone dipropionate (augmented)

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "betamethasone dipropionate" and tradename "Diprolene". The AERS database was searched for cases received through November 21, 2007.

2.3.6 Amcinonide

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "amcinonide" and tradename "Cyclocort". The AERS database was searched for cases received through November 21, 2007.

2.3.7 Betamethasone valerate

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "betamethasone valerate" and tradename "Beta-Val". The AERS database was searched for cases received through November 21, 2007.

2.3.8 Lindane

The AERS search was conducted using the MedDRA High Level Group Term "Medication Errors" and Preferred Term "Pharmaceutical Product Complaint", the active ingredient "lindane" and tradename "Kwell". The AERS database was searched for cases received through October 3, 2007.

2.4 EXPERT PANEL DISCUSSION (EPD)

The DMETS Expert Panel was consulted for their opinions about safety concerns with identifying this product as a "lotion" versus "(b) (4) The following information was presented to the group: "(b) (4) (b) (4) *[benzyl alcohol* (b) (4) *5% (w/w)] is indicated for patients infected with head lice and it is applied to the scalp, left on for 10 minutes, and then rinsed out. The Division would like to know whether it is safer to call the product a lotion or an* (b) (4) *Please tell me your thoughts as to your safety concerns about the use of lotion vs.* (b) (4) *for this product."*

2.5 PROPOSED LABELING

DMETS reviewed the insert labeling submitted to the Agency on June 15, 2007 and the container labels and carton labeling submitted to the on September 17, 2007.

3 RESULTS

3.1 DRUG FACTS AND COMPARISONS

Using the above stated search strategy (see section 2.1), DMETS identified the following drug products that are available in a lotion dosage form and to be applied to the scalp and/or have an

indication for use in the treatment of head lice: selenium sulfide 2.5% lotion, malathion lotion, lindane lotion and permethrin lotion. There were no (b) (4) identified that satisfied the aforementioned search strategy (see Section 2).

3.2 CLINICAL PHARMACOLOGY ONLINE

Using the above stated search strategy (see Section 2.2), DMETS identified the following drug products that are available in a lotion dosage form and to be applied to the scalp and/or have an indication for use in the treatment of head lice: Ala Scalp 2% lotion, betamethasone dipropionate (augmented) lotion, amcinonide 0.1% lotion, and betamethasone valerate 0.1% lotion. There were no (b) (4) identified that satisfied the aforementioned search strategy (see Section 2).

3.3 AERS

The AERS search retrieved one case which described a patient who "allegedly presented to emerency room with open sores on his arms and legs. Patient allegedly was coated from head to toe with Lindane Lotion and the lotion was not washed off." According to the report, the outcome was "death due to brain stem compromise allegedly resulting from the seizures caused by the wrongful application of Lindane."

3.4 EPD

There were a total of eight (n=8) participants in the EPD group surveyed. The group consisted of pharmacists and nurses from DMETS.

- Four participants (n=4) preferred the term " (b) (4) Two people provided comments on why they preferred (b) (4) and the remaining two witheld explanation. The comments that were provided are as follows:
    - "My only concern with using lotion as the dosage form is that people may apply it all over their bodies rather than just to the scalp"
    - "I think (b) (4) is a better name because of how I identify with the word lotion…(1) all over the body…(2) left on indefinitely (3) without adverse effect".
- Two participants (n=2) preferred the term "lotion". One provided explanation while the other did not. The comment provided is as follows:
    - "…I think it would confuse patients to call it an (b) (4) Would they know what it means?"
- Two participants (n=2) had no preference and had no concerns in either case. One participant provided explanation while the other did not. The comment provided is as follows:
    - "From strictly a safety perspective, I do not think it makes a difference. Lotions are only topical. (b) (4) can be topical or injections."

3.5 PROPOSED LABELING

3.5.1 Container Label and Carton Labeling

3.5.1.1 The dosage form and strength are printed on the same line which makes it difficult to read.

3.5.1.2 The "w/w" designation that follows the product strength may be confusing.

3.5.1.3 The wording "For topical use only" is located on the side panel where it is not readily visible. Additionally, the wording is generalized and not specific enough to this product.

3.5.1.4 Under the Dosage and Administration section on the side panel, directions are given for applying the product, however, these directions are incomplete.

3.5.1.5 The distributor's name logo is too large in size and detracts from other important information on the label such as the proprietary name, established name, and strength.

3.5.1.6 The dosing chart in the text description of the Outer Box is not included in the carton or package insert labeling so it is not clear if the sponsor intends to introduce it into the labeling for the carton and package insert.

3.5.1.7 The net quantity statement, "8 oz (227 g)", is relatively small in size and difficult to see.

3.5.2 Package Insert Labeling

3.5.2.1 A dosing chart was presented in a draft text version of the Outer Box, however, this chart is not in the actual proposed carton or insert labeling.

4 DISCUSSION

4.1 DOSAGE FORM

Our analysis did not uncover any overwhelming evidence to suggest the term "lotion" would be problematic if used as a dosage form descriptor for " (b) (4) Many similar types of products employ the term "lotion" in their name without sequelae. We did note that none of the products currently marketed for use on the scalp/hair utilize the term " (b) (4) suggesting this may not be a term patients would be familiar with.

DMETS evaluated the proposed dosage form "lotion" for its potential for error and evaluated the proposed packaging configuration of the lotion. Additionally, DMETS reviewed the packaging for several like products [selenium sulfide lotion, Ovide (malathion) lotion, lindane lotion, Beta-Val (betamethasone valerate) lotion, Diprolene lotion (betamethasone dipropionate, augmented), and amcinonide lotion (see Appendices, section 8.3)] to determine if the packaging of these products may have had an impact on the limited number of errors reported with lotions. We noted that the packaging sizes vary but all have a "screw-on" cap. Additionally, three of the products [Beta-Val (betamethasone valerate), Diprolene (betamethasone dipropionate,

augmented), and amcinonide] have a tapered opening (see section 8.3). When errors were reported, they were with products that resembled other products (i.e., ophthalmics). Thus, it appears that the use of "lotion" may not be the reason a product is applied over the body but the shape and size of the bottle may pose a greater risk. Therefore, although there appears to be no standard package or container type for these types of products, we note that the shape and size of the container are important.

4.2 SAFETY CONCERNS WITH PRODUCT LABELS AND PACKAGING

Our review of the labels and labeling submitted by the sponsor identified design issues that may result in failures in the medication use process leading to error. Of major concern is the way in which the product will be packaged. As currently proposed, the packaging of this product resembles that of an oral medication. The bottle is opaque (b) (4). Due our concerns, the sponsor proposed design changes to the container closure system. The following are the three proposals aimed at preventing accidental oral ingestion.

Container Closure Proposals:

1. (b) (4)
2. (b) (4)
3. An orifice reducing plug (b) (4) and current cap (the orifice reducer we have identified (b) (4)

(b) (4)

. Proposal three describes the use of an orifice reducing plug. This type of closure is preferable since it narrows the opening significantly and slows product flow. Additionally, this top resembles those seen for topical products rather than oral.

Although the sponsor has addressed the issue of oral ingestion, we are equally concerned with the size of the bottle and inability to provide correct dosing. Since the bottle is opaque and the usual dose is 4 ounces to 6 ounces, (b) (4)

Our analysis of the labels and labeling identified other failure modes that may lead to medication errors. Specifically, the dosage form statement is on the same line as the statement of strength. This presentation causes the statement of strength to be less prominent and visible. Rearranging this information may enhance visibility of the statement of strength. Additionally, the statement of strength is presented as "5% (b) (4). The (b) (4) may be confusing because it may be unfamiliar to some healthcare practitioners and it is typically not presented next to the numerical strength on the container label and carton labeling and may be more useful presented elsewhere in the labeling.

DMETS also notes that the wording “For topical use only” is on the side panel of the container and carton labeling but is not on the principal display panel where is would be more readily visible. Because the product has a topical route of administration, the warnings and precautions should be stronger and more readily visible on the container and carton labeling in order to avoid oral ingestion of the product or administration of the product to areas of the body other than the hair and scalp.

Additionally, the instructions for use as presented on the carton and container labeling are not complete and may therefore result in misuse of the product. This is concerning since the product is not only indicated for use in the adult patient population but the pediatric population as well.

The distributor’s name logo is prominent on the label and detracts from other important information on the container and carton labeling such as the proprietary name, established name, and product strength. Making the logo less prominent will enhance visibility of the aforementioned information. Additionally, the net quantity statement is relatively small and therefore impairs the visibility of the information.

5 CONCLUSIONS AND RECOMMENDATIONS

We have no objections to the use of the term “lotion” in the established name of (b) (4) (b) (4) However, DMETS believes that the way the product is packaged and labeled will play a crucial part in the safe and proper use of this product. The actual packaging configuration of this product and the way the information is presented on the label are important factors which can mitigate potential drug administration errors. Therefore, we recommend revising the labels and labeling as follows.

5.1 CONTAINER LABEL AND CARTON LABELING

5.1.1 We recommend implementing the third container proposal (an orifice reducing plug and current cap).

5.1.2 Relocate the dosage form statement "(b) (4) so that it immediately follows the established name (since it is part of the established name).

5.1.3 Delete the (b) (4) designation (b) (4)

5.1.4 Relocate the wording "For topical use only" from the side panel to the principal display panel and increase the size of the wording to make it more prominent on the label. Please consider rewording the statement to "For topical use on the hair and scalp only" in order to make the warning more specific. Additionally, consider adding the warning "Harmful if swallowed" and "Keep out of reach of children" to help prevent accidental oral ingestion of the product.

5.1.5 The instructions for use in the Dosage and Administration, as presented on the side panel, are incomplete. Please print a complete set of instructions for use of the product.

5.1.6 Delete the distributor's name logo or decrease its size.

5.1.7 Please clarify whether the dosing chart presented in the draft text description of the Outer Box is to be included in the actual carton and insert labeling.

5.1.8 Increase the size of the statement of strength "8 oz. (227 g)", slightly, in order to increase its visibility on the label.

5.1.9 We recommend limiting the size of the bottle to a 4 ounce bottle.

5.2 INSERT LABELING

5.2.1 See Section 5.1.6

DMETS would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. If you have further questions or need clarifications, please contact Sammie Beam, OSE Project Manager, at 301-796-0080.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

   AERS is a database application in CDER FDA that contains adverse event reports ofr approved ddrugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontenaous reporting system that captures reports from healthcare professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reorting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2007. URL: http://www.clinicalpharmacology.com. November, 2007. Accessed November 16, 2007.

3. Wickersham RM, Novak KK, Schweain SL et al, editors. Drug Facts and Comparisons. St. Louis: Wolters Kluwer Health; 2007.

4. PDR® Electronic Library™. Thomson Healthcare. http://www.thomsonhc.com (accessed December 10, 2007).

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/s/

Loretta Holmes
12/21/2007 03:43:24 PM
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Linda Kim-Jung
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