

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-794

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3 Administrative Information

1.3.1 Patent Information

Forms 3542a for the patents listed in Table 1 are located on the following pages.

Table 1: List of 5% Dapsone Topical Gel U.S. Patents and U.S. Published Patent Applications

PATENT/APPLN NO.	DESCRIPTION	EXPIRATION
5,863,560	A dermatological gel composition containing, in part, Dapsone, carbomer and ethoxydiglycol.	September 11, 2016
6,620,435	A dermatological, semisolid aqueous gel containing a pharmaceutical.	September 11, 2016
Appln 2003/0157036	A method for treatment of acne using a dermatological composition containing Dapsone.	Filed Feb 20, 2002, Published Aug 21, 2003

1.3.2 Patent Certification

Not applicable.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-794

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ACZONE™ Gel 5%

ACTIVE INGREDIENT(S)

Dapsone

STRENGTH(S)

5%

DOSAGE FORM

Topical Gel

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 5,863,560	b. Issue Date of Patent 01/26/1999	c. Expiration Date of Patent 09/11/2016
d. Name of Patent Owner Virex Corporation	Address (of Patent Owner) 2579 Midpoint Drive	
	City/State Fort Collins, Colorado	
	ZIP Code 80525	FAX Number (if available) (970) 482-9735
	Telephone Number (970) 482-5868	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Claim Number (as listed in the patent) | Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

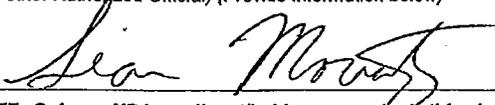
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed = 08/31/2004
-------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Sean F. Moriarty, Vice President Business Development and Counsel, Atrix Laboratories, Inc.	
Address 2579 Midpoint Drive	City/State Fort Collins, Colorado
ZIP Code 80525	Telephone Number (970) 482-5868
FAX Number (if available) (970) 482-9735	E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 21-794	
		NAME OF APPLICANT / NDA HOLDER Atrix Laboratories, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) ACZONE™ Gel 5%			
ACTIVE INGREDIENT(S) Dapsone		STRENGTH(S) 5%	
DOSAGE FORM Topical Gel			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 6,620,435		b. Issue Date of Patent 09/16/2003	c. Expiration Date of Patent 09/11/2016
d. Name of Patent Owner Virotext Corporation		Address (of Patent Owner) 2579 Midpoint Drive	
		City/State Fort Collins, Colorado	
		ZIP Code 80525	FAX Number (if available) (970) 482-9735
		Telephone Number (970) 482-5868	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
		City/State	
		ZIP Code	FAX Number (if available)
		Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

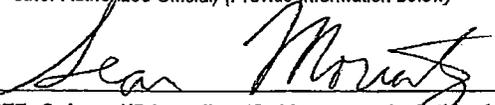
6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

08/31/2004



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Sean F. Moriarty, Vice President Business Development and Counsel, Atrix Laboratories, Inc.

Address

2579 Midpoint Drive

City/State

Fort Collins, Colorado

ZIP Code

80525

Telephone Number

(970) 482-5868

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Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-794

NAME OF APPLICANT / NDA HOLDER
Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ACZONE™ Gel 5%

ACTIVE INGREDIENT(S)
Dapsone

STRENGTH(S)
5%

DOSAGE FORM
Topical Gel

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
Appln 2003/0157036 (Filed and pending)

b. Issue Date of Patent
02/20/2002

c. Expiration Date of Patent

d. Name of Patent Owner
Atrix Laboratories, Inc.

Address (of Patent Owner)
2579 Midpoint Drive

City/State
Fort Collins, Colorado

ZIP Code
80525

FAX Number (if available)
(970) 482-9735

Telephone Number
(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Claim Number (as listed in the patent) 1-22, 24-26	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------

6. Declaration Certification

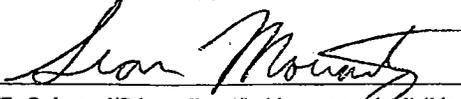
6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

08/31/2004



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Sean F. Moriarty, Vice President Business Development and Counsel, Atrix Laboratories, Inc.

Address

2579 Midpoint Drive

City/State

Fort Collins, Colorado

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Telephone Number

(970) 482-5868

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.3.10 Claimed Exclusivity [21 CFR §314.50 (j)]

5% Dapsone Topical Gel is a unique and novel drug product indicated for the topical treatment of acne vulgaris. Although dapsone is a well-characterized drug, the safety and efficacy of 5% Dapsone Topical Gel is dependent on the aqueous gel base of DGME, NF and Carbomer 980 (Carbopol). The formulation is preserved with Methylparaben, NF and is neutralized to a physiologic pH with sodium hydroxide, NF. The currently marketed formulation of dapsone is an oral tablet. 5% Dapsone Topical Gel is the first topical formulation of dapsone.

The new clinical investigations reported in this application (TD-010, TD-020, C98-D235, DAP9901, DAP9902, DAP9903, DAP9905, DAP9907, DAP9910, DAP0004, DAP0110, DAP0114, 03-0-182, DAP0203 and DAP0204) are essential to the approval of 5% Dapsone Topical Gel and were conducted by Atrix Laboratories, Inc (Atrix), by Virotext (from whom Atrix purchased the rights to 5% Dapsone Topical Gel), and by Fujisawa (on behalf of Atrix). Atrix was named as the sponsor on the FDA 1571 forms submitted to IND 54,440 for these studies. No other clinical studies have been performed using 5% Dapsone Topical Gel.

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 212-4950
<http://www.atrixlabs.com>

VIA FEDERAL EXPRESS

October 20, 2004

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

OCT 21 2004

MEGA / CDER

N-000(BM)

ORIG AMENDMENT

**RE: NDA 21-794, Amendment #003
5% Dapsone Topical Gel**

**Subject: Revised Exclusivity Statement, Additional Trade Names and Clarification
on Patient Information Leaflet Terminology**

Dear Dr. Wilkin:

A reference is made to phone calls from Commander Frank Cross Jr., Senior Regulatory Management Officer on October 14 and 15, 2004.

Enclosed is a revised statement for the claimed exclusivity. Pursuant to FDCA §505(c)(3)(D)(iii) and 21 CFR §314.108(b)(4), Atrix is claiming marketing exclusivity for three years following the approval date of Dapsone Topical Gel, 5%.

We are also submitting three proprietary names for our product and request a review of these names by the Division of Medication Errors and Technical Support (DMETS). The following table contains the information required for evaluation.

Proposed Trade Names in the Order of Priority	1) ACZONE™, ACZONE™
Established Name	5% Dapsone Topical Gel
Proposed Indication	ACZONE™ is an aqueous-based topical formulation of dapsone, USP, indicated for topical treatment of acne vulgaris.
Dosage Form, Route of Administration, and Dosing Regime	Dosage Form: Gel Route of Administration: Topical Dosing Regime: Twice daily to the face, neck, and back

ORIGINAL

EXCLUSIVITY SUMMARY

NDA # 21-794

SUPPL #

HFD # 540

Trade Name ACZONE Gel 5%

Generic Name dapstone

Applicant Name QLT USA, Inc.

Approval Date, If Known 7/7/05

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?
YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 08-6841

DAPSONE TABLET, 25MG

NDA# 08-6842

DAPSONE TABLET, 100MG

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1: DAP0203:

A 12-Week, Multicenter, Double-Blind, Randomized, Parallel-Design Study of 5% Dapsone Topical Gel and Vehicle Control in Patients with Acne Vulgaris

Investigation #2: DAP0204:

A 12-Week, Multicenter, Double-Blind, Randomized, Parallel-Design Study of 5% Dapsone Topical Gel and Vehicle Control in Patients with Acne Vulgaris

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Frank H. Cross, Jr.

Title: Project Manager

Date: July 6, 2005

Name of Office/Division Director signing form: Stanka Kukich

Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Stanka Kukich

7/7/05 10:01:51 AM

1.3.8 Waiver Requests

1.3.8.1 Request For Partial Pediatric Waiver

Per 21 CFR 314.55 (c)(3), Atrix requests a partial pediatric waiver for 5% Dapsone Topical Gel. The basis for this request is provided below.

5% Dapsone Topical Gel has not been evaluated in pediatric patients younger than 12 years of age and is not recommended for use in this patient population.

Acne vulgaris is a common skin disease with onset in adolescence, generally at puberty. Surveys among adolescents show more than an 80% incidence of manifest disease (Plewig et al. 1993). The prevalence in pre puberty pediatric patients under 12 years of age is substantially lower (Harper et al. 2003). Therefore, 5% Dapsone Topical Gel is not likely to be used in a substantial number of these patients.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-794 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 9/17/04 Action Date: _____

HFD-540 Trade and generic names/dosage form: ACZONE™ (dapson) Gel, 5%

Applicant: QLT USA Inc. Therapeutic Class: 3

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Topical treatment of acne vulgaris. Glucose 6-phosphate dehydrogenase (G6PD) levels should be obtained prior to initiating therapy with ACZONE™ Gel, 5%. In patients with a history of anemia and predisposition to increased hemolytic effect with dapson (e.g., glucose-6-phosphate dehydrogenase deficiency), closer follow-up for blood hemoglobin levels and reticulocyte counts should be implemented (see PRECAUTIONS). Alternatively, other therapies for acne than ACZONE™ Gel, 5%, may be considered.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 12 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

Formulation needed

Other: _____

Safety and efficacy was not studied in pediatric patients less than 12 years of age, therefore ACZONE™ Gel, 5%, is not recommended for use in this age group.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments:

Safety and efficacy was evaluated in 1169 children aged 12-17 years old treated with ACZONE™ Gel, 5%, in the clinical studies.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-794

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337. (revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-794
HFD-960/ Grace Carmouže

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Markham Luke

7/1/05 01:50:43 PM

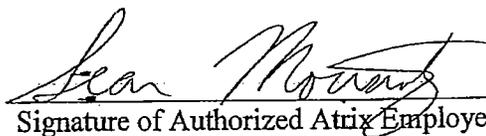
Concur with Pediatric Waiver for acne vulgaris indication in
patients up to the age of 12.

Stanka Kukich

7/5/05 11:41:26 AM

1.3.3 Debarment Certification

Atrix hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

 8/25/2004
Signature of Authorized Atrix Employee

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Steven Garrett, MS, DDS, FACD	TITLE Senior Vice President Clinical Research
FIRM / ORGANIZATION Atrix Laboratories, Inc.	
SIGNATURE 	DATE 5/17/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Steven Garrett, MS, DDS, FACD	TITLE Senior Vice President Clinical Research
FIRM / ORGANIZATION Atrix Laboratories, Inc.	
SIGNATURE 	DATE 5/17/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

VIA FEDERAL EXPRESS

July 7, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: NDA 21-794, ACZONE™ (dapson) Gel, 5%

Subject: Amendment 48: Draft Package Insert

Dear Dr. Wilkin:

Reference is made to a telephone conference held on July 7, 2005 between Commander Frank Cross, Senior Regulatory Management Officer and Stanka Kukich, M.D, Deputy Director, FDA - Cheri Jones and Hansa Isokoski, QLT USA, Inc.

The following changes were made to the Draft Package Insert:

- Added in PRECAUTIONS second half of sentence of the last paragraph:

"Psychosis was reported in 2 of 2372 patients treated with ACZONE Gel, 5%,
and in 0 of 1660 patients treated with vehicle."

There are no changes to the labeling, i.e., package insert, patient information, container tubes and cartons, from the FDA fax of 6/30/05 other than those items discussed with Dr. Kukich on 7/6/05 and 7/7/05.

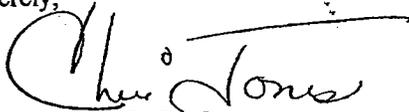
An electronic copy (Word) of the a highlighted and final labeling Word-file was e-mailed to Commander Frank Cross and are provided on a CD-ROM, sent to the CDER Electronic Document Room.

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 6/22/2005 Rev. 17 and is virus free.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qltinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,



Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

QLT USA, Inc

DATE OF SUBMISSION

07/07/2005

TELEPHONE NO. (Include Area Code)

970-482-5868

FACSIMILE (FAX) Number (Include Area Code)

970-212-4950

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

2579 Midpoint Drive
Fort Collins, CO 80525-4417

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

21-794

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Dapson

PROPRIETARY NAME (trade name) IF ANY

Aczone™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

4,4'-diaminodiphenyl sulfone

CODE NAME (if any)

DOSAGE FORM:

Gel

STRENGTHS:

5%

ROUTE OF ADMINISTRATION:

Topical

(PROPOSED) INDICATION(S) FOR USE:

Topical treatment of acne vulgaris

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (NDA, 21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b)(1)

505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Amendment 48 - Final Draft Labeling

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

n/a

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 54,440, DMF 1

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify) _____

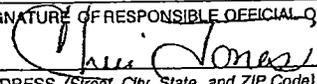
CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Cheri Jones, MS, RAC, Vice President, Regulatory Affairs	DATE 07/07/2005
ADDRESS (Street, City, State, and ZIP Code) 2579 Midpoint Drive, Fort Collins, CO 80525-4417	Telephone Number 970-212-4901	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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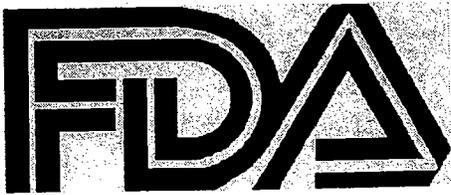
11 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 7, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of July 6 and 7, 2005, Clinical Teleconferences for NDA 21-794 ACZONE™ (dapsone) Gel, 5%	

Total no. of pages including cover: 4

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our July 6 and 7, 2005, clinical teleconferences concerning your NDA 21-794, ACZONE™ (dapsone) Gel, 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

Teleconference Date: July 6 and 7, 2005

Location: N229

NDA 21-794, Aczone (dapson topical gel) 5%

Indication: Treatment of acne vulgaris

Applicant: QLT USA Inc

Meeting Chair: Stanka Kukich, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Stanka Kukich, M.D., Deputy Director, DDDDP, HFD-540

Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

J. Steven Garrett, DDS, MS, Senior Vice President, Clinical Research

Cheri Jones, M.S., RAC, Vice President of Regulatory Affairs

Hansa Isokoski, M.S. (Pharm), Manager, Regulatory Affairs

On July 6, 2005, the following discussion took place:

Agency:

For the Package Insert for this NDA 21-794, please move the last sentence under ADVERSE REACTIONS Section to PRECAUTIONS, Section, General Sub-section, and add an additional sentence, i.e.:

“In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE™ Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE™ Gel, 5%, and in 0 of 1660 patients treated with vehicle.”

Applicant:

The applicant agreed to make the requested changes and will submit an amendment to the NDA to that effect.

On July 7, 2005, a follow-up teleconference took place with Ms. Cheri Jones:

Agency:

For the Package Insert for this NDA 21-794, please add the following phrase to the end of the last sentence of PRECAUTIONS, Section, General Sub-section:

“and in 0 of 1660 patients treated with vehicle.”

Therefore, for PRECAUTIONS Section, General Sub-section, the revised wording should be:

“In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE™ Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE™ Gel, 5%, and in 0 of 1660 patients treated with vehicle.”

Applicant:

The applicant agreed to make the requested change and will submit an amendment to that effect

The teleconferences ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Frank Cross
7/7/05 10:43:57 AM
CSO

Stanka Kukich
7/7/05 12:55:34 PM
MEDICAL OFFICER

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/s/

Frank Cross
7/7/05 01:11:28 PM
CSO
Faxed to applicant on 7/7/05



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 7, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of July 5, 2005, Clinical Teleconference for NDA 21-794 ACZONE™ (dapsone) Gel, 5%	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our July 5, 2005, clinical teleconference concerning your NDA 21-794, ACZONE™ (dapsone) Gel, 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: July 5, 2005
DRUG: Aczone (dapson) Gel, 5%
NDA: 21-794
SPONSOR: QLT USA, Inc.
Steve Garrett, M.D., Clinical
Cheri Jones, Vice President, Regulatory Affairs
Hansa Isokoski, Regulatory Affairs
FDA: Stanka Kukich, M.D., Deputy Division Director, DDDDP/540
Brenda Vaughan, M.D., Medical Officer, DDDDP/540
Mary Jean Kozma-Fornaro, Supervisor, Project Management Staff/
DDDDP/540
Subject: NDA 21-794 Phase 4 Commitment

The sponsor was contacted to obtain agreement to revision of the Clinical Phase 4 Commitment previously agreed to on July 1, 2005.

The revised and agreed to Clinical Phase 4 commitment is as follows:

Conduct a randomized, blinded, cross-over safety study with each acne patient treated with ACZONE Gel, 5% for 12 weeks and vehicle for 12 weeks with at least a two week washout period in at least 50 evaluable G6PD deficient patients with acne vulgaris to further evaluate the risk of hematological adverse events with use of ACZONE Gel, 5% in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Obtain baseline, week 2, and end of each 12 week treatment period laboratory testing including complete blood count, reticulocyte counts, haptoglobin, and LDH levels. Plasma dapson levels, and N-acetyl dapson levels should be obtained at baseline, week 2, and at the end of each 12 week treatment period. Additionally, plasma dapson and its metabolite levels should be obtained in relation to adverse events which may be considered dapson related.

Study Protocol Submission: November 1, 2005
Study Initiation: March 1, 2006
Final Study Report Submission: January 1, 2008

Sponsor will submit an official statement of agreement to the Clinical Phase 4 commitment as documented in this memorandum of telephone conference.

Conversation ended amicably.

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/s/

Mary Jean Kozma Fornaro
7/6/05 12:27:14 PM
CSO

Stanka Kukich
7/7/05 09:31:49 AM
MEDICAL OFFICER

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/s/

Frank Cross
7/7/05 01:09:55 PM
CSO
Faxed to applicant on 7/7/05



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 7, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of June 30, 2005, Clinical Teleconferences for NDA 21-794 ACZONE™ (dapson) Gel, 5%	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our June 30 2005, clinical teleconference concerning your NDA 21-794, ACZONE™ (dapson) Gel, 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

Teleconference Date: June 30, 2005

Time: 2:30 p.m.

Location: N225

NDA 21-794, Aczone (dapsona topical gel) 5%

Indication: Treatment of acne vulgaris

Applicant: QLT USA Inc

Meeting Chair: Stanka Kukich, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Stanka Kukich, M.D., Deputy Director, DDDDP, HFD-540

Markham C. Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540

Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540

Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DBIII, HFD-725

Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

J. Steven Garrett, DDS, MS, Senior Vice President, Clinical Research

Cheri Jones, M.S., RAC, Vice President of Regulatory Affairs

Hansa Isokoski, M.S. (Pharm), Manager, Regulatory Affairs

Mohammed Azab, M.D., M.B.A, Executive Vice President, Research and Development and Chief Medical Officer

Craig Wesselman, Ph.D., Biostatistician III

With reference to the applicant's Agency's June 30, 2005 (Applicant's amendment #40), the following discussion took place:

Agency:

As reviews for this NDA have closed your amendment has not been reviewed. Please re-submit this amendment for our review after you have received our NDA action letter.

Applicant:

The applicant appreciated the feedback and will re-submit the amendment as advised.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Frank Cross
7/7/05 09:49:29 AM
CSO

Stanka Kukich
7/7/05 10:00:10 AM
MEDICAL OFFICER

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/s/

Frank Cross

7/7/05 01:08:08 PM

CSO

Faxed to applicant on 7/7/05



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

VIA FEDERAL EXPRESS

July 6, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: NDA 21-794, ACZONE™ (dapsone) Gel, 5%

Subject: Amendment 47: Draft Package Insert 07/06/05

Dear Dr. Wilkin:

Reference is made to a telephone conference held on July 6, 2005 between Commander Frank Cross, Senior Regulatory Management Officer and Stanka Kukich, M.D, Deputy Director, FDA - Steve Garrett, Cheri Jones and Hansa Isokoski, QLT USA, Inc, and an e-mail dated July 6, 2005 to Cheri Jones including a Word-file of the draft package insert faxed to QLT USA, Inc. on June 30, 2005 (DRAFT Package Insert 06/29/05):

The following changes were made to the Draft Package Insert:

- Moved from ADVERSE REACTIONS:

A sentence in lines 308-310 after Table 4 to the last paragraph of the PRECAUTIONS section, starting line 144 (see below for the 1st added sentence).

- Added in PRECAUTIONS as the last paragraph:

"In the clinical trials, a total of 12 out of 4032 patients were reported to have depression (3 of 1660 treated with vehicle and 9 of 2372 treated with ACZONE™ Gel, 5%). Psychosis was reported in 2 of 2372 patients treated with ACZONE Gel 5%."

There is no change to patients with depression as for the patient discussed in the teleconference of July 6, 2005, no depression was reported.

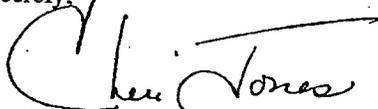
An electronic copy (Word) of the labeling Word-file e-mailed to Commander Frank Cross are provided on a CD-ROM, which was sent to the CDER Electronic Document Room.

**APPEARS THIS WAY
ON ORIGINAL**

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 6/22/2005 Rev. 17 and is virus free.

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qltinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,

A handwritten signature in cursive script that reads "Cheri Jones". The signature is written in black ink and is positioned above the printed name.

Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

CONSULTATION RESPONSE		
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT		
OFFICE OF DRUG SAFETY		
(DMETS; HFD-420)		
DATE RECEIVED: Oct. 15, 2004	DESIRED COMPLETION DATE: December 25, 2004 PDUFA: July 7, 2005	ODS CONSULT #: 04-0277
TO: Jonathan Wilkin, M.D. Director, Division of Dermatologic and Dental Drug Products HFD-540		
THROUGH: Frank Cross Project Manager, Division of Dermatologic and Dental Drug Products HFD-540		
PRODUCT NAME: Aczone [™] (Dapsone Topical Gel) 5% NDA# 21-794	SPONSOR: Atrix Laboratories, Inc.	
SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.		
RECOMMENDATIONS:		
<ol style="list-style-type: none"> 1. DMETS has no objections to the use of the proprietary name, Aczone[™]. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. 2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product. 3. DDMAC finds the proprietary name Aczone acceptable from a promotional perspective. 		
<hr/> Carol Holquist, R.Ph. Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 Fax: (301) 443-9664		

**APPEARS THIS WAY
ON ORIGINAL**

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 5, 2005
NDA NUMBER: 21-794
NAME OF DRUG: Aczone™
(Dapsone Topical Gel)
5%
NDA SPONSOR: Atrix Laboratories, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products, for an assessment of the proprietary name "Aczone" regarding potential name confusion with other proprietary or established drug names. The container labels, carton and package insert labeling for Aczone were reviewed for possible interventions that will minimize medication errors.

PRODUCT INFORMATION

Aczone™ is the proposed name for dapsone, a topical gel indicated for the treatment of acne vulgaris in patients twelve years of age and older. A thin layer of the product is applied to the acne affected areas of the skin twice daily after skin is gently washed. Aczone™ will available in strength of 5%, and supplied in a 30 gram tube.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference textsⁱ as well as several FDA databasesⁱⁱ for existing drug names which sound-alike or look-alike to "Aczone™" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Databaseⁱⁱⁱ and the data provided by Thomson & Thomson's SAEGIS™ Online Service^{iv} were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal

ⁱ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2005, and the electronic online version of the FDA Orange Book.

^{iv} WWW location <http://www.uspto.gov>.

^v Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

APPEARS THIS WAY
ON ORIGINAL

prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Aczone. Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed names Aczone.
2. The Expert Panel identified five proprietary names that have potential for confusion with Aczone. These products are listed in Table 1 along with the dosage forms available and usual dosage (see below).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Aczone

Product Name	Dosage form(s), Established Name	Usual adult Dose*	Other**
Aczone (Rx)	Dapsonone Topical Gel 5%	Apply a thin layer to the acne affected areas of skin twice daily after skin is gently washed and rub in gently and completely.	
Acson (Rx)	Perindopril Tablets 2 mg, 4 mg, and 8 mg	Initially, 4 mg once daily or in divided doses. Titrate; max 16 mg/day.	**L/A
AK-Con (Rx)	Naphazoline Solution 0.1%	Instill 1 or 2 drops into the conjunctival sac of affected eye every 3 to 4 hours, up to 4 times daily.	**L/A, S/A
Actos (Rx)	Pioglitazone Tablets 15 mg, 30 mg, and 45 mg	Initially 15 mg or 30 mg once daily. Max 45 mg/day.	**L/A, S/A
Azdone (Rx)	Aspirin and Hydrocodone Tablets 500 mg/5 mg	Take 1 to 2 tablets every 4 to 6 hours as needed; max 8 per day.	**L/A, S/A
Accuzyme (Rx)	Papain and Urea Ointment 8.3 x 10 ⁵ units/10%	Gently clean wound with Allclenz® wound cleanser. Apply Accuzyme to clean applicator, and apply directly to wound. Cover area with appropriate dressing. Daily or twice daily applications are preferred.	**L/A

*Frequently used, not all-inclusive.

**L/A (look-alike), S/A (sound-alike)

**APPEARS THIS WAY
ON ORIGINAL**

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary names were converted into their phonemic representation before they run through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Aczone were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Aczone with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Aczone (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> <i>Aczone</i> <i>Bid qd</i> <i>#1</i>	Aczone, use twice a day as directed, dispense 1 tube.
<u>Inpatient RX:</u> <i>Aczone b.i.d. qd</i>	

2. Results:

One responded in the written study interpreted the proposed name, Aczone as "Aczime", and another participant interpreted the proposed name as "Aczyme", which are similar to Accuzyme, a currently marketed product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

APPEARS THIS WAY
ON ORIGINAL

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Aczone", the primary concerns raised were related to five look-alike and/or sound-alike names currently marketed in the United States. The products considered to have potential for name confusion with Aczone were: Aceon, AK-Con, Actos, Azdone, and Accuzyme. Upon further review of the names gathered from EPD and POCA, the names AK-Con and Actos were not reviewed further due to a lack of convincing look-alike/sound-alike similarities, in addition to differentiating product characteristics such as dosage form, route of administration, and dosing regimen.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Aczone and the aforementioned names. It should be noted, however, that two participants in the written study identified the proposed name as Aczme and Aczynie, which are similar to the product, Accuzyme. The majority of the remaining incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Aczone.

1. Aceon was identified to look-similar to the proposed name, Aczone. Aceon contains the active ingredient perindopril, and is indicated for the treatment of hypertension. The recommended dose is 4 mg once daily or in two divided doses. The dose may be titrated up to a maximum of 16 mg per day. The look-alike similarities between the names can be attributed to the presence of the letter combinations "Ac" and "on" in each name. Both names also contain the letter "e", although in different positions. Additionally, the presence of the letter "z" in Azdone does help to somewhat distinguish the names from each other. This difference is more prominent, however, if the letter is written with a down stroke. Both products can be administered twice daily. However, Aceon and Aczone differ in route of administration (oral vs. topical), dosage form (tablets vs. topical gel), indication of use (hypertension vs. acne), and strength (2 mg, 4 mg, and 8 mg, vs. 5%). Additionally, because Aceon is available in multiple strengths, a strength would likely be indicated on a prescription order prior to dispensing, unlike Aczone, which is available in only one strength, and can be dispensed without a strength being indicated. DMETS believes that the numerous product differences such as route of administration, dosage form, indication of use, and product strength, minimize the potential for risk and confusion between Aceon and Aczone.

Aceon

Aczone

Aceon Aczone

2. Azdone was identified to have look-alike and sound-alike similarities to Aczone. Azdone is a Class III controlled narcotic medication, which contains the active ingredients hydrocodone and aspirin, and is indicated for the treatment of pain. The look-alike and sound-alike similarities between the names can be attributed to the overlapping letters "A", "z", "o", "n", and "e", which appear in each name. Additionally, both names are two syllable words that consist of six letters. The "d" in the name "Azdone", if written with a prominent upstroke, can help to distinguish the names from each other when written. However, when spoken, the letter "d" can be somewhat muffled. Azdone and Aczone have overlapping numerals in their strengths (500 mg/5 mg vs. 5%). However, the products differ in route of administration (oral vs. topical), dosage form

APPEARS THIS WAY
ON ORIGINAL

(tablet vs. topical gel), dosing regimen (every 4 to 6 hours vs. twice daily), and indication of use (pain vs. acne). A search of the Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com, revealed that the last recorded year of sales for Azdone in the United States was 1997. At that time, the sales value indicator was indicated as low. Further research revealed that Azdone does not appear in a number of hard copy and on-line references, including the 2004 Red Book, the on-line version of the Orange Book and Facts and Comparisons, or in on-line drug search engines, such as www.Rxlist.com. Also, per the on-line Orange Book, there are no generic equivalents of Azdone currently marketed. DMETS believes that the product differences, in addition to the fact that Azdone is no longer marketed in the United States, nor does it appear in current references; minimize the concern regarding potential confusion and errors between Azdone and Aczone.

Azdone

Aczone

Azdone Aczone

3. Accuzyme was identified to look similar to Aczone. Accuzyme contains papain and urea in an ointment formulation. It is indicated for the debridement of necrotic tissue and slough in acute and chronic lesions such as pressure ulcers, varicose, diabetic, and decubitus ulcers, burns, and postoperative wounds. After cleaning, the ointment is applied directly to the wound and covered with the appropriate dressing. The orthographic similarities stem from the fact that both names begin with the letter combination "Ac" and the letter "z". The ending letter combination of each name also looks similar, particularly when scripted ("me" vs. "ne"). Both products are available in one strength, thus prescription orders can be written, and the medication dispensed without a strength being indicated. In addition, the products share an overlapping route of administration (topical), and dosing regimen (twice daily). The products differ in indication (wound debridement vs. acne). When written, the names are visibly different from each other in length, and the presence of the down stroke letter "y", if prominent, helps to further distinguish the names. Although both products can be used twice daily, Accuzyme is often used after surgical procedures, for the cleansing of wounds, unlike Aczone, which will be applied daily until clear for the treatment of acne. DMETS feels that the differences in indication, context of use, in addition to the minimal look-alike similarity between the names, will minimize potential for confusion and errors between Accuzyme and Aczone.

Accuzyme

Aczone

Accuzyme Aczone

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of Aczone, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (3 gram Professional Sample and 30 gram tube.)

1. *2*

7

APPEARS THIS WAY
ON ORIGINAL

2. Please ensure that the established name is at least ½ the size of the proprietary name, per 21 CFR 201.10(g)(2).
3. Relocate the net quantity away from the product strength.
4. The company logo is distracting. Please decrease its prominence and relocate it away from the proprietary name and product strength.

B. CARTON LABELING

See comments under container label.

C. PACKAGE INSERT LABELING



IV. RECOMMENDATIONS

- A. DMETS has no objections to the use of the proprietary name, Aczone. This is considered a tentative decision, and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- B. DMETS requests submission of the labels and labeling for review when available.
- C. DDMAC finds the proprietary name Aczone acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph., M.S.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A. DMETS prescription study results for Aczone

Inpatient	Outpatient	Voicemail
Aczine	Aczone	Aczone
Aczine	Acyone	Actzone
Aczine	Acyone	Axone
Aczine	Acyone	Axone
Aczine	Aczine	Axone
Aczine	Aczone	Axonne
Aczine	Aczone	Axsome
Aczine	Aczone	Axum
Aczone	Aczone	Axzone
Aczone	Aczone	
Aczone	Aczone	
	Aczynie	

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

/s/

Tia Harper-Velazquez
2/28/05 08:53:17 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/28/05 09:54:15 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/28/05 04:13:03 PM
DRUG SAFETY OFFICE REVIEWER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: July 1, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063

Subject: Facsimile Transmission of Post Marketing Commitment for NDA 21-794 ACZONE™ (dapson) Gel, 5%

Total no. of pages including cover: 2

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

Document to be mailed: YES NO

Please provide us with your response to the below post marketing commitment for your NDA 21-794, ACZONE™ (dapson) Gel, 5% :

Conduct a randomized, blinded, cross-over safety study with each acne patient treated with ACZONE Gel for 12 weeks and vehicle for 12 weeks with at least a two week washout period in at least 50 evaluable G6PD deficient patients with acne vulgaris to assess the safety of ACZONE Gel, 5%, in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Obtain baseline and end of each 12 week treatment period laboratory testing including complete blood count, reticulocyte count, haptoglobin and LDH levels. Plasma dapson levels and N-acetyl dapson levels should also be obtained at baseline and at the end of each 12 week treatment period and in relation to adverse events which may be considered as dapson-related.

Study Protocol Submission: November 1, 2005
Study Initiation: March 1, 2006
Final Study Report Submission: January 1, 2008

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
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www.qltinc.com

ORIG AMENDMENT

NI-000-81

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JUL 01 2005

MEGA / CDER

VIA FEDERAL EXPRESS

June 30, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

JUN 30 2005

HFD-540/CDER

RE: NDA 21-794, Aczone (dapson) Gel, 5%

Subject: Amendment 41: 3 Gram and 30 Gram Tube and Carton Printed Labels

Dear Dr. Wilkin:

Reference is made to a telephone conversation held between Commander Cross, FDA, and Cheri Jones and Hansa Isokoski, QLT USA, Inc. on June 29, 2005 regarding final labeling for the 3 gram and the 30 gram tubes and cartons.

Electronic PDF copies of the labeling files are provided. Electronic copies were included on a CD-ROM, which was sent to the CDER Electronic Document Room.

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 6/29/2005 Rev. 8 and is virus free.

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qtlinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,

Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

5 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-2

11 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 3



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Labeling for NDA 21-794, ACZONE™ (dapsone) Gel, 5%	

Total no. of pages including cover: 12

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our labeling for your NDA 21-794, Aczone™ (dapsone) Gel, 5%.

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Coordinator
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

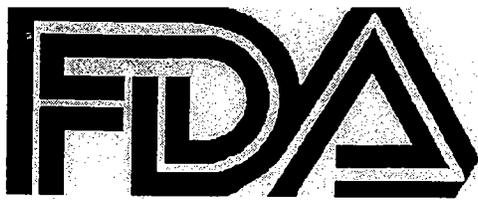
11 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-4



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 30, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063

Subject: Facsimile Transmission of Post Marketing Commitment for NDA 21-794 ACZONE™ (dapsone) Gel, 5%

Total no. of pages including cover: 2

Document to be mailed: YES NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

Document to be mailed: YES NO

Please provide us with your response to the below post marketing commitment for your NDA 21-794, ACZONE™ (dapsone) Gel, 5% :

Conduct a blinded cross-over safety study with each acne patient treated with ACZONE Gel for 12 weeks and vehicle for 12 weeks with at least a two week washout period in at least 50 evaluable G6PD deficient patients with acne vulgaris to assess the safety of ACZONE Gel, 5%, in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Obtain baseline and end of each 12 week treatment period laboratory testing including complete blood count, reticulocyte count, haptoglobin and LDH levels. Plasma dapsone levels and N-acetyl dapsone levels should also be obtained at baseline and at the end of each 12 week treatment period and in relation to adverse events which may be considered as dapsone-related.

Study Protocol Submission: November 1, 2005
Study Initiation: March 1, 2006
Final Study Report Submission: January 1, 2008

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qitinc.com

VIA FEDERAL EXPRESS

June 28, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: NDA 21-794, Aczone (dapson) Gel, 5%

**Subject: Amendment 39: Final Draft Labeling for Cartons and Tubes
Request for one time 3 Gram Tube Exemption**

Dear Dr. Wilkin:

Reference is made to a telephone and e-mail conversation held on June 28, 2005 between FDA – Frank Cross and QLT – Cheri Jones.

Enclosed as requested are:

- Revised final draft labeling for the 3 gram and 30 gram tubes and cartons with the language requested by the Agency in the 6/22/05 communication (Tab A), Rev 6/28/04.
- The name of the marketing partner has been updated from Fujisawa Healthcare, Inc. to Astellas Pharma USA, Inc. on all labeling components.
- Note is made of the discussion with Commander Cross regarding the Agency's concurrence that the requested "Return to Carton" and "from light" are omitted due to the structure of the 3 gm tube
- Copy of the printed 3 gm Physician Sample tube (Rev. 6/05) for which QLT requests a one-time exemption. (Tab B).

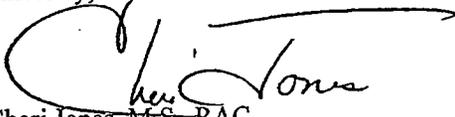
Electronic copies (Word) of the labeling files are provided on a CD-ROM, which was sent to the CDER Electronic Document Room.

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version Check: 9.0.0.338 with current virus definitions dated 6/22/2005 Rev. 17 and is virus free.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qfinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,

A handwritten signature in black ink, appearing to read "Cheri Jones". The signature is written in a cursive style with a long, sweeping horizontal line extending to the right.

Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

8 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-5



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

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VIA FEDERAL EXPRESS

June 30, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: NDA 21-794, ACZONE™ (dapson) Gel, 5%

Subject: Amendment 40: Official Submission of an E-mail Request dated June 30, 2005 on G6PD Deficiency Screening and Proposed Labeling Language

Dear Dr. Wilkin:

Reference is made to e-mail conversations between Commander Cross, the Agency, and Cheri Jones on June 30, 2005 on screening for Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency and the labeling language in Indications and Precautions sections. Enclosed is a copy of the e-mail from Cheri Jones to Commander Frank Cross (Tab A).

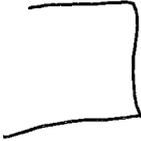
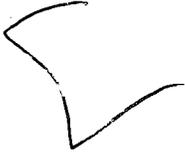
We have found that commercial kits from _____ are approved to screen for G6PD deficiency. This screening test could be done in a doctor's office. Attached please find descriptions of commercially available screening tests (Tab B). The manufacturer and distributor, _____ has confirmed that screening kits available in all States.

_____ has a test (Procedure No. 203) to screen a patient for G6PD deficiency. If the results indicate that the patient is G6PD deficient, they recommend measuring the level of deficiency, using Procedure No. 345-UV.

- o If a patient is positive upon screening, a quantitative blood draw for the G6PD levels and a full blood count would be run.
- o For those patients who are negative on screening, ACZONE™ treatment could be prescribed.

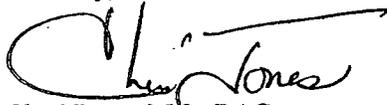
QLT USA, Inc. request the following change in the package insert:

APPEARS THIS WAY
ON ORIGINAL



If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qltinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,



Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT QLT USA, Inc.	DATE OF SUBMISSION 06/30/2005
TELEPHONE NO. (Include Area Code) 970-482-5868	FACSIMILE (FAX) Number (Include Area Code) 970-212-4950
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 2579 Midpoint Drive Fort Collins, CO 80525-4417	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-794		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Dapsone	PROPRIETARY NAME (trade name) IF ANY Aczone™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 4,4'-diaminodiphenylsulfone	CODE NAME (If any)	
DOSAGE FORM: Gel	STRENGTHS: 5%	ROUTE OF ADMINISTRATION: Topical
(PROPOSED) INDICATION(S) FOR USE: Topical treatment of acne vulgaris		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (NDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601).
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER _____
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION: Amendment 40 - G6PD Screening
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED: _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

n/a

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 54,440, DMF _____

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input checked="" type="checkbox"/>	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input type="checkbox"/>	20. OTHER (Specify) _____

CERTIFICATION

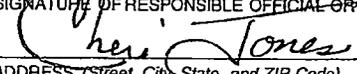
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Cheri Jones, MS, RAC, Vice President, Regulatory Affairs	DATE 06/30/2005
ADDRESS (Street, City, State, and ZIP Code) 2579 Midpoint Drive, Fort Collins, CO 80525-4417	Telephone Number 970-212-4901	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------

From: Cheri Jones
Sent: Thursday, June 30, 2005 8:15 AM
To: 'CROSSF@cder.fda.gov'
Subject: One Last Request for dapsone NDA

Good Morning, Frank:

We have found that commercial kits are approved to screen for G6PD deficiency. This screening test could be done in a doctor's office.

- o If a patient is positive upon screening, a quantitative blood draw for the G6PD levels and a full blood count would be run.
- o For those patients who are negative on screening, ACZONE treatment could be prescribed.

We would like to request that you present this to Drs. Luke and Vaughan prior to our 2:30 pm telecon today and ask them if it is possible to discuss this screening for 5 minutes before discussing the phase IV commitment.

The net affect, we believe, to the Package Insert **Indications** and **Precautions** language is illustrated below:



We are aware of a kit distributed commercially in the U.S. by _____, that is qualitative and gives you a plus or minus reading.

I know this is the 11th hour but it is hugely important to the viability of this therapy in the market and still identifies those patients at risk for G6PD deficiency.

Can you please see if we can discuss this issue prior to Phase IV study with the medical reviewers?

Your assistance in getting this before them would be greatly appreciated.

Cheri

Cheri Jones, M.S., RAC

Regulatory Affairs

970-212-4901

6 Page(s) Withheld

2 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 6



FACSIMILE TRANSMITTAL SHEET

DATE: June 22, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Post Marketing Commitment for NDA 21-794 ACZONE™ (dapson) Gel, 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Document to be mailed: YES NO

Please provide us with your response to the below post marketing commitment for your NDA 21-794, ACZONE™ (dapson) Gel, 5% :

Conduct an open-label safety study of 12 months duration in at least 300 evaluable G6PD deficient patients with acne vulgaris to assess the safety of ACZONE Gel, 5%, in this population. Patients with rarer genetic abnormalities such as methemoglobin reductase or the congenital methemoglobinemias may also be studied. Blood laboratory monitoring including complete blood count, reticulocyte count and evaluation of other manifestations of hemolysis should be conducted to rule out hemolysis with use of ACZONE Gel, 5%. Plasma dapson levels and N-acetyl dapson levels should also be obtained on a scheduled basis and in relation to adverse events which may be dapson-related.

Study Protocol Submission:	6 months after approval date
Study Initiation:	8 months after approval date
Final Study Report Submission:	30 months after approval date

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 22, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Labeling for NDA 21-794, ACZONE™ (dapsone) Gel, 5%	

Total no. of pages including cover: 24

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our labeling for your NDA 21-794, Aczone™ (dapsone) Gel, 5%. Revised text for the carton/container labeling and your original proposed carton/container labeling is also attached to this facsimile transmission.

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Coordinator
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

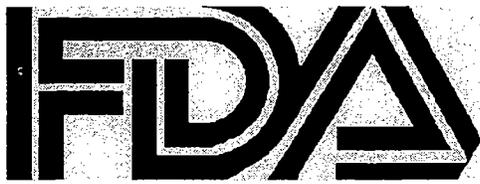
23 Page(s) Withheld

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X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-7



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 22, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of June 20, 2005, CMC Teleconference for NDA 21-794 ACZONE™ (dapson) Gel, 5%	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our June 20, 2005, CMC teleconference concerning your NDA 21-794, ACZONE™ (dapson) Gel, 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

Teleconference Date: June 20, 2005

Time: 1200

Location: N229

NDA 21-794, Aczone™ (dapson) Gel, 5%

Topical Treatment of Acne vulgaris

Sponsor: QLT USA Inc.

Discussion of CMC Issues

Meeting Chair: Ernie Pappas

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Ernie Pappas, Chemistry Reviewer, DNDCIII, HFD-830

Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

QLT USA Inc:

Cheri Jones, M.S., RAC, Director, Regulatory Affairs

Lynn Hansen, CMC Regulatory Affairs

Hansa Isokoski, Regulatory Group Leader

With reference to the June 14, 2005, teleconference, and the June 20, 2005, submission, the following comments were conveyed:

Agency:

Chemistry, Manufacturing and Controls:

1. While the drug substance in the drug product is within the _____% specification limits, the inconsistent drug substance within this specification is inconsistent for the pilot batches assayed. The applicant should revise its specification for release testing of commercial batches to perform ' _____ of the drug product and submit a prior approval commitment to that effect. After a sufficient amount of information has been amassed, the applicant may submit a prior approval supplement to delete this specification.
2. The particle size justification submitted on June 20, 2005, is acceptable.

Applicant:

The applicant agreed to submit the referenced prior approval commitment to the NDA in the next few days.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Frank Cross
6/22/05 02:54:24 PM
CSO

Ernest G. Pappas
6/22/05 02:56:46 PM
CHEMIST



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 22, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of June 14, 2005, CMC Teleconference for NDA 21-794 ACZONE™ (dapson) Gel, 5%	

Total no. of pages including cover: 5

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our June 14, 2005, CMC teleconference concerning your NDA 21-794, ACZONE™ (dapson) Gel, 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

MEMORANDUM OF TELECON

DATE: 6/14/05, 2:00 P.M.

APPLICATION NUMBER: NDA 21-794

DRUG PRODUCT: ACZONE (dapsone topical gel) 5%

BETWEEN:

Name: Cheri Jones , M.S., RAC, Vice President Regulatory Affairs
Hansa Isokoski , M.S. (Pharm) RAC, Manager Regulatory Affairs
Lynn Hansen , Manager Regulatory Affairs
Brent Coonts , B.S. Biochemistry, Director AMDS (Analytical Methods
Development & Services)
Dennis Wilson , B.S. Chemistry, Scientist I - AMDS

Phone: (970) 212-4901
Representing: QLT USA, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Ramesh Sood, Ph.D., Chemistry Team Leader
Ernest Pappas, Chemistry Reviewer
Margo Owens, Regulatory Project Manager

SUBJECT: NDA 21-794

The teleconference was requested by FDA to discuss CMC issues related to the submitted NDA.

The following discussion took place:

- The Agency stated that information sent earlier proposed a revision of the specification. There needs to be a separate test for homogeneity and the proposed acceptance criteria for the particle size distribution will need to be justified based on the data. The homogeneity testing requested for dapsone content is a routine test for topical products. The Applicant needs to perform testing on bulk/release and during stability.

The Applicant stated that they believe they have done testing on bulk. They asked whether The Agency is proposing the same during stability.

- The Agency stated that homogeneity should be monitored during stability studies also. The USP Content Uniformity acceptance criterion of 85-115% may be used in guiding

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Withheld Track Number: Administrative- *1A*

NDA 21-794

The Applicant indicated that they would provide the requested information by close of business on Friday, June 17, 2005.

The conversation ended amicably.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Margo Owens
6/22/05 10:50:01 AM
CSO

Ramesh Sood
6/22/05 11:06:08 AM
CHEMIST



ORIGINAL

QLT USA, Inc. 2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

VIA FEDERAL EXPRESS

June 22, 2005

N-cod(C)
NEW CORRESP

RECEIVED
JUN 23 2005
MEGA / CDER

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RE: NDA 21-794, Aczone (dapson) Gel, 5%

Subject: Amendment 37: Official Submission of Labeling Word Files E-Mailed to Commander Frank Cross on June 7, 2005

Dear Dr. Wilkin:

Reference is made to a telephone conversation held on June 22, 2005 between FDA – Frank Cross and QLT – Hansa Isokoski.

Electronic copies (Word) of the labeling Word files e-mailed to Commander Frank Cross are provided on a CD-ROM, which was sent to the CDER Electronic Document Room.

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 6/22/2005 Rev. 17 and is virus free.

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qtlinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,


Cheryl Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

8 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

8



QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

DUPLICATE

VIA FEDERAL EXPRESS

June 27, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

RECEIVED

JUN 28 2005

MEGA / CDER

NEW CORRESP

N-000-C

RE: NDA 21-794, Aczone (dapsone) Gel, 5%

Subject: Amendment 38: Official Submission of an E-mail dated 6-26-05 and the Attached Document and Labeling Word Files E-Mailed to Commander Frank Cross on June 26, 2005

Dear Dr. Wilkin:

Reference is made to an e-mail from Cheri Jones to Commander Frank Cross dated June 26, 2005. The e-mail, with attachments, is submitted as an official submission to NDA 21-794.

Electronic copies (Word) of the labeling Word files e-mailed to Commander Frank Cross are provided on a CD-ROM, which was sent to the CDER Electronic Document Room.

QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 6/22/2005 Rev. 17 and is virus free.

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@qtlinc.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Our fax number is 970-212-4950.

Sincerely,

Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

Cc. Commander Frank Cross, Jr., Senior Regulatory Management Officer

From: Cheri Jones
Sent: Sunday, June 26, 2005 4:49 PM
To: 'CROSSF@cder.fda.gov'
Subject: Amendment 038, Draft Labeling, Post Approval Commitment

Dear Frank:

Further to the teleconference of Friday, June 24th regarding the labeling for the dapsons NDA, we herewith attach, as agreed, the redline strikeout version of our proposed draft package insert, rationale support labeling changes, proposal for postmarketing study commitment, and 3 gram professional sample labeling for tube.

Attached you will find:

- 1) **Revised Draft Package Insert and Patient Information**
- 2) **Rationale for G6PD-related suggested labeling changes**
- 3) **Post Approval Commitment - Phase IV Draft Protocol Synopsis:**

"A Phase I, Randomized, Cross-Over Study of ACZONE™ Gel, 5%, and Vehicle Control in Patients with G6PD deficiency"

- 4) **3 gram Professional Sample tube** side-by-side comparison of "at risk" labeling printed and recommended draft labeling from Agency.

Please note that we have two issues with the proposed language for this sample tube:

1) _____

2) _____

3) We request a one time exemption to use these Sample tubes as there are only minor differences between "at risk" and proposed language. We will, however, make all changes to the carton into which the 10 tubes are packaged. No commercial tubes were printed.

This information will be officially submitted as Amendment 038 to the NDA on Monday, 6/27/05.

We confirm the telecon for 4 PM Eastern time.

The dial-in number for this call is: **866-542-9023; Access Code: 3570056#**

Participants - QLT

Mohammed Azab, M.D., Executive VP, R&D and Chief Medical Officer
Dr. Steve Garrett, Sr. VP Clinical Research
Cheri Jones, VP Regulatory Affairs
Hansa Isokoski, Mgr Regulatory Affairs

Astellas:

Joy Rico, M.D., VP Medical Science

James Keirns, Sr Dir, Biopharmaceutical Sciences

We are most hopeful that prior to the PDUFA date of 7/7/05, we can achieve agreement on labeling. There is a strong desire by the medical team wishing that you invite Dr. Wilkin to this telecon, if at all possible.

We would appreciate the review team's thoughts on how we can move toward a resolution of the labeling and plans for action on this NDA by the end of the meeting.

I think that you will probably want to assemble the entire team for this telecon as the revisions to the insert cover most review disciplines.

Please contact me if you have any difficulty with these attachments or need to contact me: 970-212-4901 or 970-227-5814 (Blackberry).

I look forward to a very productive discussion and meeting. Hope we can move this NDA forward.

Cheri

Cheri Jones, M.S., RAC

Regulatory Affairs

970-212-4901

17 Page(s) Withheld

X Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-9



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical Information Requests Regarding NDA 21-794, ACZONE™ (dapson) Gel, 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please provide a response to the following clinical information requests regarding your NDA 21-794, Aczone™ (dapson) Gel, 5%:

1. The number of patients from all studies with peripheral neuropathy reported as an AE. Also provide a peripheral neuropathy listing sorted by study arm (Vehicle or Active) that includes patient number and study number.
2. The location in the submission of one table that lists all serious AEs for all studies. If not available, please provide by tomorrow (June 22, 2005).

3. Provide reticulocyte counts for all G6PD deficient patients sorted by study arm (active or vehicle).

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Coordinator
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: May 27, 2005

TO: Frank Cross, Regulatory Project Manager
Brenda Vaughan, Medical Officer
Division of Dermatologic and Dental Drug Products, HFD-540

THROUGH: Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-794

PROTOCOL(s): DAP0203 and DAP 0204
A 12-Week, Multicenter, Double-blind Randomized, Parallel-Design
Study of 5% Dapsone Topical Gel and Vehicle Control in Patients with
Acne Vulgaris

SPONSOR: QLT USA Inc.

DRUG: Dapsone

INDICATION: Acne Vulgaris

**CHEMICAL
CLASSIFICATION:** 3

**THERAPEUTIC
CLASSIFICATION:** S

INSPECTION SUMMARY GOAL DATE: May 16, 2005

ACTION GOAL DATE: July 7, 2005

I. BACKGROUND:

In this NDA application, the sponsor included results of protocols DAP 0203 and DAP 0204 for the use of dapsone in the treatment of acne vulgaris.

The objective of the study was to assess the safety and efficacy of 5% Dapsone Topical Gel treatment in patients with acne vulgaris. Subjects were seen on an outpatient basis.

These inspections of the sites of _____ were requested by the reviewing division because these sites had high rates of efficacy in comparison with other centers.

The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
_____	_____	_____	11 Feb 05	7 Apr 05	NAI/011468
_____	_____	_____	11 Feb 05	25 Apr 05	VAI/011489
_____	_____	_____	11 Feb 05	25 May 05	VAI/03805

Site # 42



See **Overall Assessment and Recommendations**, below

- a. 59 subjects were enrolled to the study with two subjects dropping out of the study. Consent forms were present and signed appropriately for all subjects. Source documents for nine of the enrolled subjects were reviewed in depth including, but not limited to, visit dates, efficacy evaluations, concomitant medications, abnormal laboratory results, and adverse event reporting.
- b. There were no limitations to the inspection.
- c. A Form 483 was not issued.

Site # 8



See Overall Assessment and Recommendations, below

- a. 44 subjects were screened for the study, and 27 subjects completed the study. Consent forms were present for all subjects. Records of nine subjects were reviewed in depth including, but not limited to, inclusion/exclusion criteria, adverse events, concomitant medications, and drug accountability.
- b. There were no limitations to the inspection.
- c. A Form FDA 483 was issued. The first observation noted that safety and efficacy assessments were recorded by the study coordinator in violation of the protocol which required that study site personnel responsible for conducting the safety and efficacy assessments should not handle the study medication, and, similarly, drug accountability assessments and study drug weight assessments should be conducted by a person not involved with the safety and efficacy assessments. Since the study coordinator was responsible for maintaining drug accountability, she should not have been involved in safety and efficacy assessments. However, her handwriting did appear on Acne Lesion Count Worksheets which is part of the safety and efficacy assessment. The clinical investigator addressed this observation in a note to the file which he signed stating that the study coordinator did not assess acne lesions or acne adverse events and only recorded the findings of the clinical investigator.

The second observation regarding a lack of drug accountability appeared to be the result of confusion over the calibration and operation of the scale used to weigh the test article upon dispensation and return. This confusion resulted in obviously erroneous information being recorded regarding the weight of the study article at dispensation and return since its weight at dispensation could not be less than its weight at return. We recommend for this reason that data from the following subjects be excluded from the safety and efficacy analysis since their compliance with the treatment regimen cannot be verified: 0426, 0009, 0013, 0014, 0015, 1128, 1028, 0428, 0429, 1173, and 0543.

Site # 17



See Overall Assessment and Recommendations, below

- a. 12 subjects were enrolled study. Records for all 12 subjects were reviewed in depth including medical histories, physicals, lesion counts, drug accountability records, randomization reports, and adverse event reports. No serious adverse events were reported.
- b. There were no limitations to the inspection.
- c. A Form FDA 483 was issued with two observations noting that six subjects had comedone counts exceeding the maximum allowed by protocol and four subjects received topical drugs on the face during the 28 day washout period prior to baseline.

The protocol required that study subjects have a clear diagnosis of acne vulgaris as defined by having 20-50 inflammatory lesions (pustules and papules) and 20-100 comedones above the mandibular line at Baseline. Subjects 1252, 1253, 1256, 1258, 1376, and 1377 had comedone counts exceeding the upper limit specified by protocol. Subjects 1253 and 1376 had pustule/papule counts less than the lower limit specified by protocol but were enrolled in the study.

The protocol also required that subjects not use topical agents anywhere on the face for 28 days prior to Baseline and throughout the study. Subjects 1251, 1252, 1256, and 1258 reported the use of topical agents within the 28 day period preceding Baseline but were enrolled in the study.

We recommend that data regarding study subjects 1251, 1252, 1253, 1256, 1258, 1376, and 1377 be excluded from the overall safety and efficacy analysis for this study.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For _____ site, there was sufficient documentation to assure that all audited subjects did exist, fulfill the eligibility criteria, received the study medication, and had the primary efficacy endpoint captured as specified in the protocol. The data submitted in support of this application by _____ appear adequate in support of the relevant submission.

For _____ site, we recommend that data from the subjects noted above be excluded from the safety and efficacy analysis since it is not possible to assess the compliance of these subjects with the treatment regimen as described in the protocol.

For [redacted] site, we recommend that data from those subjects noted above who violated protocol limits on numbers of comedones and papules/pustules or used topical drugs be excluded from the safety and efficacy analysis. The data for the remaining subjects for [redacted] and [redacted] appear acceptable in support of the relevant indication.

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

cc:
HFD-580/Doc. Rm. NDA 21-794
HFD-45/Program Management Staff (electronic copy)
HFD-46/RF
HFD-46/c/r/s
HFD-46/Blay

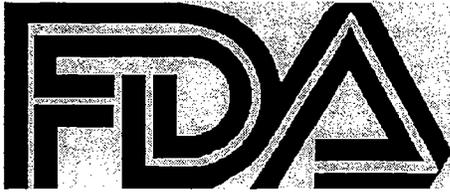
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this page is the manifestation of the electronic signature.**

/s/

Roy Blay
5/27/05 04:14:50 PM
CSO

Ni Aye Khin
5/27/05 04:21:58 PM
MEDICAL OFFICER



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V**

FACSIMILE TRANSMITTAL SHEET

DATE: May 19, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Chemistry, Manufacturing and Control Information Requests Regarding NDA 21-794, ACZONE™ (dapsone topical gel) 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Document to be mailed: YES NO

Information requests from our Chemistry, Manufacturing and Controls reviewer follows:

1. Under section 3.2.P.3.4 (Module 3 Volume 3) titled "Controls of Critical Steps and Intermediates [5% Dapsone Topical Gel]":

The critical processing steps — should have a temperature range control to ensure control the size and extent of crystals during manufacturing instead of the proposed "... at or below -0°C...".

2. Under section 3.2.P.5.1 titled "Specification [Dapsone Topical Gel]", the regulatory release specification 26005C.005 and the regulatory shelf-life specification 26005B.005 for the 5% Dapsone Topical Gel product should be revised as follows:

- a) The appearance attribute should be described as being a "Uniform glossy gritty gel with uniform distributed suspended particles" instead of " —————".
- b) The specification for particle size should be revised to accurately reflect the particle size distribution found from data derived for Particle Size of 5% Dapsone Topical Gel (Document # 50916.001 R). Therefore, it is recommended that acceptance criteria in the specification for the following particle sizes be proposed as:

Mean % particles _____ and less
Mean % particles _____ and less
Mean % particles _____ and less
Maximum particle size (µm) equal to NMT _____

3. Under section 3.2.P.5.2 titled "Analytical Procedures [Dapsone Topical Gel]", the sample chromatogram for HPLC Analytical Method _____, should identify the related impurities relative to the retention time of Dapsone and the area % given under the chromatogram for the related impurities relative to the peak area of Dapsone. This is an improvement to the SOPs which aids the analyst in comparing the reference chromatogram to the sample chromatogram of the HPLC analysis for 5% Dapsone Gel.
4. Under section 3.2.P.5.2 titled "Analytical Procedures [Dapsone Topical Gel]", Test Method T314.004, article 5.3.1, it is stated that " _____
_____ However, when we spread a sample on white paper, no particles could be seen. In this regard, it was observed by us that uniformly distributed fine drug particles were visible only when the sample is spread on a glass slide. Please revise your test method to include spreading of sample on a glass slide or other appropriate surface that can clearly show the suspended particles.
5. Please provide all available data that show the amount of API that remains dissolved in the vehicle at release and over the shelf life. Since the safety and efficacy of the product may be affected by the amount of the API that remains dissolved, we recommend that you include acceptance criterion for the dissolved API in the regulatory specification based on the available data.

Please provide a response to the above issues no later than June 7, 2005

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Coordinator
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cderr.fda.gov

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

/s/

Frank Cross
5/19/05 01:25:31 PM
CSO
Faxed to applicant on 5/19/05.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

Date: May 18, 2005
To: Frank Cross, Project Manager
Division of Dermatological and Dental Drug Products
From: Iris Masucci, PharmD
Suzanne Berkman, PharmD
Division of Drug Marketing, Advertising, and Communications
Subject: Drug: Aczone (dapsons topical gel 5%)
NDA: 21-794

DDMAC has reviewed the proposed PI, Carton/Containers, and Physician Sample for Aczone and offer the following comments. Please let us know if you have any further questions, comments, or need further clarification.

PACKAGE INSERT

CLINICAL PHARMACOLOGY - Pharmacokinetics

- 
- 



CLINICAL STUDIES

- 
- 
- 



3 Page(s) Withheld

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Withheld Track Number: Administrative- 10

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/s/

Suzanne Berkman
5/18/05 08:35:07 AM
DDMAC REVIEWER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-794	Efficacy Supplement Type N/A	Supplement Number N/A
Drug: ACZONE™ (dapsone) Gel, 5%		Applicant: QLT USA, Inc.
RPM: Cross	HFD-540	Phone # 301-827-2020
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	3	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 	N/A	
❖ User Fee Goal Dates		
July 7, 2005		
❖ Special programs (indicate all that apply)		
<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	<input checked="" type="checkbox"/> Paid UF ID number <u>4655</u>	
<ul style="list-style-type: none"> • User Fee waiver 	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) _____ N/A	
<ul style="list-style-type: none"> • User Fee exception 	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) <u>N/A</u>	
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<ul style="list-style-type: none"> • This application is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	

<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> OC clearance for approval 	N/A
<ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. 	(X) Verified
<ul style="list-style-type: none"> ❖ Patent 	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) () Verified 21 CFR 314.50(i)(1) () (ii) () (iii) N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p>	(X) N/A (no paragraph IV certification) () Verified N/A () Yes () No N/A () Yes () No N/A

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No N/A

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)

- Exclusivity summary
- Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

No

- Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

Yes, Application # _____
 No

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent applicant-proposed labeling	Yes
• Original applicant-proposed labeling	Yes
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	Yes
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
• Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Yes
• Applicant proposed	Yes
• Reviews	Yes
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes (in Applicant correspondence and Action Letter)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Yes – 12/18/00
• Pre-NDA meeting (indicate date)	Yes – 4/7/04
• Pre-Approval Safety Conference (indicate date; approvals only)	Yes – 6/9/05
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	7/5/05
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	4/27/05, 7/7/05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	6/29/05
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	7/6/05
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	7/6/05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	7/5/05
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	5/19/05
❖ Biopharmaceutical review(s) (indicate date for each review)	6/3/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	6/10/05
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	7/1/05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	7/1/05
• Review & FONSI (indicate date of review)	7/1/05
• Review & Environmental Impact Statement (indicate date of each review)	7/1/05
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	3/14/05
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	5/23/05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	5/16/05
❖ CAC/ECAC report	4/28/05

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease, etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: April 21, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical Information Requests Regarding NDA 21-794, ACZONE™ (dapsone topical gel) 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Document to be mailed: YES NO

An information request from our clinical reviewer follows:

For Study DAP0114, (Original Submission, Mod 5, Vol. 76, Appendix 2.5):

Compliance/Drug Concentration data on pg. 53 of 96 indicates that Patient 1424 had blood draws at BL, months 1, 3, 6, 9, & 12; however, dapsone plasma levels are not available for Months 6, 9, & 12 (revised Study DAP0114). Please explain this discrepancy.

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: April 20, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Chemistry, Manufacturing and Controls (CMC) and Clinical Information Requests Regarding NDA 21-794, ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Document to be mailed: YES NO

Information requests from our CMC and Clinical reviewers follow:

CMC:

Please submit a sample of the drug under review to the undersigned as a desk copy. Cover letter (only) of desk copy should be officially submitted.

Clinical

Regarding ECG results:

Please identify type of intraventricular conduction delay for Patients 205, 223, & 224 (Study DAP9903, Mod. 5, Vol 3, Synopsis, pg. 46, ECG Result Table). Were ECGs performed in any other studies submitted to the NDA? If so, please provide location of these data in the NDA.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



NDA 21-794

QLT USA Inc.
Attention: Cheri Jones, MS, RAC
Vice President, Regulatory Affairs
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Dear Ms. Jones:

Please refer to your August 31, 2004, new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Aczone (dapson topical gel) 5%.

We also refer to the teleconference between representatives of your firm and the FDA on February 11, 2005. The purpose of the teleconference was to discuss a clinical concern with the NDA.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Division Director
Division of Dermatologic and Dental Drug
Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Teleconference Date: February 11, 2005

Time: 12:00 p.m.

Location: N229

NDA 21-794, Aczone (dapson topical gel) 5%

Indication: Treatment of acne vulgaris

Applicant: QLT USA Inc

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540

Markham C. Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540

Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Cheri Jones, M.S., RAC, Vice President of Regulatory Affairs

Hansa Isokoski, M.S. (Pharm), Manager, Regulatory Affairs

Agency:

Please provide the Agency with data showing the correlation between blood levels of topical and systemic dapson and hemolysis to answer the question of what is the minimum amount of dapson exposure to cause a safety problem of hemolysis. This is a critical issue for our safety assessment. Please do an algebraic comparison between drug levels of dapson or its major metabolite in G6PD deficient patients. Ultimately, we need to ascertain at what systemic level of dapson exposure does hemolysis occur.

We are also interested in a breakdown of the data for those patients who are homozygous or heterozygous for G6PD deficiency.

An early look at the efficacy of this product appears to show some efficacy that may be statistically significant. Since the delta of effect between the product and vehicle is relatively small, we will be weighing the safety very carefully.

Applicant:

We will provide this analysis in the very near future.

The teleconference ended amicably.

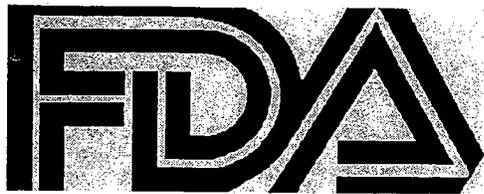
Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Jonathan Wilkin
4/19/05 01:45:03 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V**

FACSIMILE TRANSMITTAL SHEET

DATE: April 12, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063

Subject: Facsimile Transmission of Pharmacology/Toxicology Information Request Regarding NDA 21-794, ACZONE™ (dapsone topical gel) 5%

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

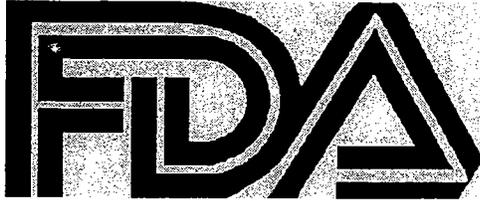
Please submit additional data concerning survival of control animals to help with analysis of data from the rat carcinogenicity study submitted to NDA 21-794. Data is needed concerning the percentage of male control rats that were still alive during week 100, and the percentage of female control rats still alive during week 92. The data should come from several recently conducted two-year carcinogenicity studies that utilized the same strain of rat as did study No. 128-002 (the two-year rat study submitted to NDA 21-794, also referred to as study No. ATLS-123). You should be able to obtain these data from the laboratory that conducted the study.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liason
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V**

FACSIMILE TRANSMITTAL SHEET

DATE: April 12, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical Information Requests Regarding NDA 21-794, ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please provide the following:

Studies DAP0203 and DAP020:

1. Tabular summary of adverse events (systemic and local AEs) and laboratory abnormalities by duration of treatment in weeks as follows: up to 12 weeks (± 3 days), patients treated >3-4 months, and patients treated >4-6 months sorted by study arm and G6PD status for the ITT population. Discuss any differences noted between each group and G6PD status.

Study DAP0114:

2. Case Report Form, G6PD status, and patient narrative for Patient 0410 (Study DAP0114).

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liason
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: March 28, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical Information Request Regarding NDA 21-794, ACZONETM (dapsone topical gel) 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please submit a revised complete Integrated Summary of Safety for your NDA 21-794, ACZONETM (dapsone topical gel) 5%.

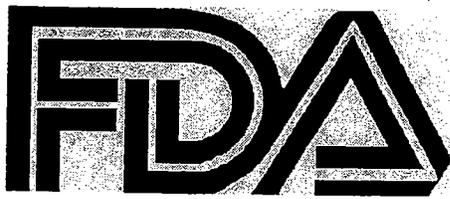
Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liason
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: March 11, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Minutes of February 25, 2005, Teleconference Regarding NDA 21-794, ACZONE™ (dapsons topical gel) 5%	
Total no. of pages including cover: 4	

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our minutes of our February 25, 2005, teleconference during which we discussed our February 9, 2005, facsimile transmission regarding your NDA 21-794, ACZONE™ (dapsons topical gel) 5%.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liason
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

Teleconference Date: February 25, 2005

Time: 1:30 p.m.

Location: N225

NDA 21-794, Aczone (dapsona topical gel) 5%

Indication: Treatment of acne vulgaris

Applicant: QLT USA Inc

Meeting Chair: Markham Luke, M.D., Ph.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Markham C. Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540

Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540

Frank H. Cross, M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

QLT USA, Inc.:

J. Steven Garrett, DDS, MS, Senior Vice President, Clinical Research

Cheri Jones, M.S., RAC, Vice President of Regulatory Affairs

Hansa Isokoski, M.S. (Pharm), Manager, Regulatory Affairs

Elyse Wolff, MT (ASCP), Director, Technical Affairs

Fujisawa HealthCare, Inc.:

Joyce Rico, M.D., Senior Medical Director, Research and Development

With reference to the Agency's February 9, 2005, facsimile transmission, the following discussion took place:

Applicant:

The Applicant requested clarification of "homozygous" from the Clinical Pharmacology/Biopharmaceutics information request #3:

- "3. The sponsor is requested to include a discussion explaining relationship between the levels of dapsona and its metabolites in G6PD deficient patients in relation to the amount of drug used, surface area treated (maximal usage condition) and possible hemolytic AEs (specifically those homozygous for mutant genes)."

Agency:

This request is to provide data for those male or female patients who are most sensitive to hemolysis due to dapsona, e.g., those patients who are homozygous for the X-linked recessive G6PD deficiency. Further, it was discussed that the serum or blood levels of dapsona in relationship to any observed hemolysis are important.

On providing any new study data, we request that the Applicant provide both qualitative and quantitative data in a tabular format for ease of review.

Applicant:

The Applicant agreed to submit the requested data by March 4, 2005.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Frank Cross
3/10/05 09:16:11 AM
CSO

Markham Luke
3/10/05 10:08:43 AM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: February 25, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Pharmacology/Toxicology Comment for NDA 21-794 ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 2

Document to be mailed: YES NO

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Document to be mailed: YES NO

A clarification of our February 9, 2005, Information Request - Pharmacology/Toxicology, for your NDA 21-794, ACZONE™ (dapson topical gel) 5%, follows:

Pharmacology/Toxicology:

Please disregard the portion of our request that pertains to survival of the Tg.AC animals:

1. Electronic copies of the reports of the two carcinogenicity studies that were submitted (two-year rat assay and mouse Tg.AC assay) in accordance with the draft guidances "Providing Regulatory Submissions in Electronic Format - General Considerations, October 2003 and "Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions, Posted August 2003
2. Historical control data concerning the mean life spans of untreated animals of the types used in the two carcinogenicity studies (e.g., mean number of weeks of survival, and the standard deviation). The data should be specific to the strains and vendors of the animals used in the studies, and have been obtained within the last five years. The sponsor should be able to obtain such data from the contract labs that performed the studies.

NDA 21-794, ACZONE™ (dapson topical gel) 5%
Facsimile Transmission of Pharmacology/Toxicology Comment
Page 2

If this data have already been submitted, please indicate exactly where those data may be found in the submission.”

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091
E-mail: crossf@cder.fda.gov

QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

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FEB 23 2005

MEGA / CDER

VIA FEDERAL EXPRESS

February 22, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

CONFIDENTIAL

**Subject: NDA 21-794, Amendment #014
5% Dapsone Topical Gel
120-Day Safety Update Report**

N-000(Su)
ORIG AMENDMENT

Dear Dr. Wilkin:

Pursuant to Section 21 CFR §314.50(d)(5)(vi)(b), this letter certifies that a review of new animal and clinical data reveals no new information about the 5% Dapsone Topical Gel product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

If you have any questions or require further information regarding this submission, please contact me by phone (970-212-4901) or at our secure email at cjones@atrixlabs.com, or Hansa Isokoski, Manager, Regulatory Affairs, by phone (970-212-4974). Please note our new fax number 970-212-4950.

Sincerely,



Cheri Jones, M.S., RAC
Vice President, Regulatory Affairs

CC. Commander Frank Cross, Jr., Senior Regulatory Management Officer

ORIGINAL

1.4 Prescribing Information

1.4.1 Package Insert and Patient Information Leaflet

**APPEARS THIS WAY
ON ORIGINAL**

34 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 11



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063

Subject: Facsimile Transmission of Chemistry, Manufacturing and Controls Reviewer Comments From Review of Proposed Generic Name for NDA 21-794 ACZONE™ (dapson topical gel) 5%

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Chemistry, Manufacturing and Controls reviewer comments from our review of your proposed generic name for your NDA 21-794 ACZONE™ (dapson ———) 5%, follows:

1. If your proposed trade name is for the drug substance only, the generic name could be one of the following two presentations.

Aczone gel (dapson gel) 5% Or Aczone (dapson) Gel, 5%

2. If the trade name is for the drug product, which is rarely the case, the generic name could only be the following presentation

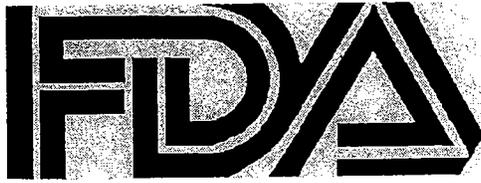
Aczone (dapson gel) 5%

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
 CDR, USPHS Commissioned Corps
 Senior Regulatory Management Officer and IT Liaison
 Division of Dermatologic and Dental Drug Products
 Office of Drug Evaluation V
 Center for Drug Evaluation and Research
 U.S. Food and Drug Administration
 Ph.# 301-827-2063/2020
 Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V

FACSIMILE TRANSMITTAL SHEET

DATE: February 16, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Biostatistical Information Request for NDA 21-794 ACZONE™ (dapsona topical gel) 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

A Biostatistical Information Request for your NDA 21-794, ACZONE™ (dapsona topical gel) 5%, follows:

Biostatistical:

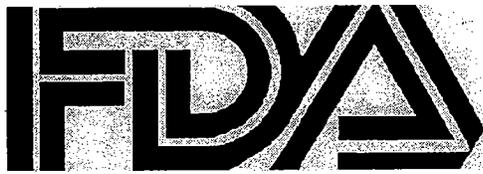
When resubmitting the datasets to incorporate the "missing" dapsona concentrations, please include a variable which identifies which observations were submitted in the initial submission and which observations are "new". Please ensure that identifying variables such as subject number and visit number are consistent with other datasets for the corresponding study so that datasets can be easily merged within a study.

Please call me when you receive this facsimile transmission. Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



FACSIMILE TRANSMITTAL SHEET

DATE: February 9, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Pharmacology/Toxicology, Clinical Pharmacology/Biopharmaceutics and Biostatistical Information Requests for NDA 21-794 ACZONE™ (dapsone topical gel) 5%	

Total no. of pages including cover: 3

Document to be mailed: YES NO

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Document to be mailed: YES NO

Pharmacology/Toxicology, Clinical Pharmacology/Biopharmaceutics and Biostatistical Information Requests for your NDA 21-794, ACZONE™ (dapsone topical gel) 5%, follow:

Pharmacology/Toxicology:

Please submit the following:

1. Electronic copies of the reports of the two carcinogenicity studies that were submitted (two-year rat assay and mouse Tg.AC assay) in accordance with the draft guidances "Providing Regulatory Submissions in Electronic Format - General Considerations, October 2003 and "Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions, Posted August 2003
2. Historical control data concerning the mean life spans of untreated animals of the types used in the two carcinogenicity studies (e.g., mean number of weeks of survival, and the standard deviation). The data should be specific to the strains and vendors of the animals used in the studies, and have been obtained within the last five years. The sponsor should be able to obtain such data from the contract labs that performed the studies.

If this data have already been submitted, please indicate exactly where those data may be found in the submission.

Clinical Pharmacology/Biopharmaceutics:

It appears from Amendment # 006 submitted on January 19, 2005, of the original NDA 21-794 submitted on August 31, 2004, that significant changes have been made in the PK studies DAP0110, DAP0114 and 03-0182. This new information will involve considerable review time towards completing the NDA. Therefore:

1. The sponsor is requested to submit modified versions of the above study reports along with the associated SAS transport data files electronically to expedite review process.
2. In the new submission, the sponsor is requested to submit line listings as well as summary of levels of dapsonsone and its metabolites in all G6PD deficient patients identified in all the PK/Clinical studies. Also, the sponsor needs to clarify how G6PD deficiency was determined.
3. The sponsor is requested to include a discussion explaining relationship between the levels of dapsonsone and its metabolites in G6PD deficient patients in relation to the amount of drug used, surface area treated (maximal usage condition) and possible hemolytic AEs (specifically those homozygous for mutant genes).

All of the above requested Clinical Pharmacology/Biopharmaceutics information should be received within 2 weeks from receiving this facsimile transmission.

Biostatistical:

Certain datasets do not provide adequate label documentation for some of the variables. In addition, some datasets use different variable names and formats which limits the ability to merge datasets. Please resolve the following dataset issues by resubmitting the following datasets (in SAS transport format) and documentation.

1. For Study 114:

Please resubmit the datasets DAPCONC and NACETYL including the variables SUBNO and VISIT_NU that are compatible with the other datasets from Study 114. Also, please provide adequate documentation defining the variables and coding for these two datasets (variable tables).

2. For Studies 203 and 204:

Please resubmit the datasets DAP0203C, DAP0203U, DAP0204C, and DAP0204U including the variables SUBNO and VISIT_NU that are compatible with the other datasets from Studies 203 and 204. Also, please include the treatment assignments (D_TRT and TRT). Provide adequate documentation defining the variables and coding for these datasets (variable tables). Please explain the difference in content between the "C" and "U" datasets.

3. For Study 004:

Please explain the difference in content between LABS and LABS1 and provide adequate documentation defining the variables and coding for these datasets (variable tables).

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov

ORIGINAL

QLT USA, Inc. 2579 Midpoint Drive
Fort Collins, CO, USA 80525-4417

Regulatory Affairs
t 970.212.4901
f 970.212.4950
www.qltinc.com

RECEIVED

FEB 17 2005

MEGA / CDER

VIA FEDERAL EXPRESS

February 16, 2005

Jonathan Wilkin, MD, Director
Food and Drug Administration
Division of Dermatologic and Dental Drug Products
Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

N-000(C)
NEW CORRESP

RE: NDA 21-794, Amendment #010
5% Dapsone Topical Gel

Subject: Response to the Filing Letter dated November 18, 2004 – Revised Draft
Labeling

Dear Dr. Wilkin:

A reference is made to the filing letter dated November 18, 2004.

Enclosed is the revised package insert as requested in the filing letter dated November 18, 2005. Additionally the company's name was changed from Atrix Laboratories, Inc. to QLT USA, Inc. No changes were made to the tube or carton labeling.

Question	Response
Filing Letter dated November 18, 2004	
Clinical Microbiology 	Enclosed are: Tab A: Revised package insert Tab B: Package insert with changes marked Tab C: Revised annotated package insert Tab D: Annotated package insert with changes marked Tab E: Revised annotated patient information leaflet Tab F: Annotated patient information leaflet with changes marked

The above-mentioned documents are also provided in PDF- and Word-documents on a CD-ROM, which was sent to the CDER Electronic Document Room. QLT USA, Inc. certifies that the CD-ROM has been scanned for viruses using Symantec AntiVirus Corporate Edition version 9.0.0.338 with current virus definitions dated 1/12/2005 Rev. 16 and is virus free.

23 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 12

MEMORANDUM

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

DATE: January 21, 2005

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Products
HFD-540

VIA: Frank Cross, Regulatory Health Project Manager
Division of Dermatologic and Dental Products
HFD-540

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Aczone (dapson topical gel) Gel 5%, NDA 21-794

The patient labeling which follows represents the revised risk communication materials of the patient information (patient package insert or PPI) for Aczone (dapson topical gel) Gel 5%, NDA 21-794. We have simplified the wording, made it consistent with the product labeling (PI), removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on labeling (PI) submitted by the sponsor on September 7, 2004. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

We also have the following comment:

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

4 Page(s) Withheld

 Trade Secret / Confidential

X Draft Labeling

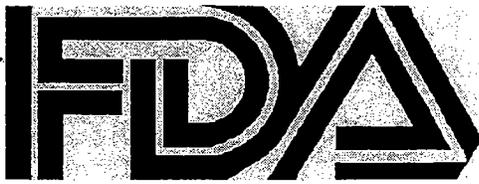
 Deliberative Process

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

/s/

Jeanine Best
1/21/05 09:25:35 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/21/05 12:11:16 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



FACSIMILE TRANSMITTAL SHEET

DATE: January 19, 2005

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: QLT USA Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical/Biostatistical Information Requests for NDA 21-794 ACZONE™ (dapsona topical gel) 5%	

Total no. of pages including cover: 4

Document to be mailed: YES NO

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Document to be mailed: YES NO

Clinical and biostatistical reviewer comments regarding your January 4, 2005, electronic mail, and your January 19, 2005, submission regarding our November 17, 2004, filing letter for your NDA 21-794, ACZONE™ (dapsona topical gel) 5%, follow:

Clinical:

- Agency clinical request 1 from November 17, 2004, filing letter: "An updated Table of Contents for Module 2 and 5 that provides the location of specific volumes (e.g. ol.1 of the ISS is located in Module 5, Vol. 87, and Vol. 22 referred to the ISS Table of Contents is located in Module 5, Vol. 104 C, etc.)."

Applicant Question:

"Revised Module 5 TOC was submitted to the NDA in Amendment #005 on November 15, 2004. We are planning on referring to Amendment #005 for the Module 5 TOC in the filing letter response. Is this acceptable? Expanded Module 2 TOC will be included in the filing letter response."

Agency:

The Applicant's proposal is acceptable.

2. Agency clinical request 4 from November 17, 2004, filing letter: "All Case Report Forms (CRF) sorted by abnormality for all subjects with abnormal hematology and serum chemistry results and the subject with allergic contact dermatitis from Study C98-D235. Additional CRFs and data may be requested as the review proceeds."

Applicant Question:

"Does the reviewer need all of these CRFs? For all Studies, 3950 of 4587-patients (86.1%) have at least one hematology or chemistry laboratory abnormality (i.e. above or below the normal range). Enclosed is a listing by study of each laboratory parameter for which at least one subject had a value outside the normal range. Submission of the CRFs for these subjects would approximately include 200 volumes containing 400 pages each. We propose to send the requested CRFs electronically as PDF documents sorted by study number and provide a cross-reference list sorted by laboratory abnormality. Since this submission would be quite voluminous, would the Agency like to modify the request? QLT USA, Inc. is also receptive to discussing alternative strategies or formats for providing this information that may facilitate the Agency's review. Options may include specific patient profiles, listings or focused tabulations."

Agency:

Please submit CRFs of those subjects with suggestions of anemia (low hemoglobin or low hematocrit) that could be attributed to dapson from the Phase 2 and 3 vehicle controlled studies and the long term safety study. The file format for archival purposes should be PDF.

3. Clinical information request from December 3, 2004, facsimile transmission: "Please provide all available baseline and endpoint photographs for all subjects with IGA scores of 0 or 1 at endpoint. We understand that photographs were uniformly taken only at specific clinic sites."

Applicant Question:

"There will be 6 photographs for each patient (2 side photos and one front for the baseline and the end of the study). There will be 96 patients with photographs (48 vehicle, 48 dapson). QLT USA, Inc. would like to send the photos in a searchable electronic format. Is this acceptable to the Agency? If submitted electronically, is PDF format acceptable? If printed photos are required, how many copies of each photo are needed?"

Agency:

Please submit the photographs in a searchable pdf format in the patient CRF PDF files. No printed photographs are needed at this time. However, individual photographs may be requested in the future.

Biostatistical:

1. Agency biostatistical request 1 from November 17, 2004, filing letter: "Copies of all items previously submitted as MS Word XP files (i.e., protocols, Variables Tables etc.) in PDF format."

Applicant Question:

"A CD-ROM was sent to the Central Electronic Document Room in Amendment #002 dated September 15, 2004. The CD ROM included PDF-copies of the following documents: ISS; ISE; Draft PI; Draft PIL; Annotated labeling; Clinical study reports, protocols and amendments for DAP0004, DAP0114, DAP0203 and DAP0204; Variables tables for SAS transport files for DAP0004, DAP0114, DAP0203, DAP0204, PK Studies, and the 2-year carcinogenicity study ATLS-123. We plan to reference Amendment #002 in the filing letter response. Is this strategy acceptable?"

Agency:

The Agency has received the referenced submission. However, the submission was not submitted per Agency guidance (Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs). Please resubmit the referenced submission following the guidance for submitting CRFs in the older formats, so that the CRFs will be organized into individual patient ID files and the CRFs will have a TOC with a hyperlink to each patient's CRF file submitted. This will greatly facilitate the review of the submission when reviewing specific patient CRFs.

2. Agency biostatistical request 2 from November 17, 2004, filing letter: "Please submit additional details regarding how the randomization was carried out in Studies DAP0203 and DAP0204 including, what information was relayed to the third party and how the third party identified the appropriate randomization number. Please identify whether the randomization was done within centers or across centers and explain why there are many gaps in the randomization sequence (unused subject numbers) and why subject numbers were not always assigned in ascending order relative to the date of randomization."

Applicant Question:

"The response was submitted in Amendment #005 dated November 15, 2004. We plan to reference Amendment #005 in the filing letter response. Is this strategy acceptable?"

Agency:

This strategy is acceptable. Please submit an additional desk copy of SN 005.

3. Agency biostatistical request 3 from November 17, 2004, filing letter: "Additional details regarding whether small centers were pooled in the analyses in Studies DAP0203 and DAP0204. If the small centers were pooled for the analysis, please provide the list of centers that were combined."

Applicant Question:

"The response was submitted in Amendment #005 dated November 15, 2004. We plan to reference Amendment #005 in the filing letter response. Is this strategy acceptable?"

NDA 21-794, ACZONE™ (dapson topical gel) 5%

Facsimile Transmission of Clinical/Biostatistical Reviewer Comments

Re: Applicant's January 4, 2005, electronic mail and January 19, 2005, submission

Page 4

Agency:

This strategy is acceptable.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT (ASCP)
CDR, USPHS Commissioned Corps
Senior Regulatory Management Officer and IT Liaison
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Ph.# 301-827-2063/2020
Fax.# 301-827-2075/2091

E-mail: crossf@cder.fda.gov



FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2004

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: Atrix Laboratories, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Clinical Information Requests for NDA 21-794, ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Clinical information requests for your NDA 21-794, ACZONE™ (dapson topical gel) 5%., follow

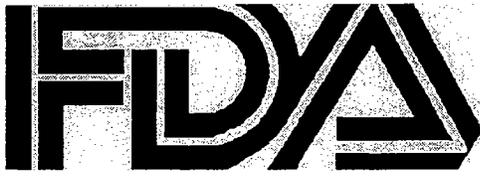
1. Please provide all available baseline and endpoint photographs for all subjects with IGA scores of 0 or 1 at endpoint. We understand that photographs were uniformly taken only at specific clinic sites.
2. Please inform as to how G6PD patients were identified for the clinical studies.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT(ASCP), CDR
 Senior Regulatory Management Officer and IT Liaison
 DDDDP, ODEV, CDER
 U.S. Food and Drug Administration



FACSIMILE TRANSMITTAL SHEET

DATE: October 26, 004

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory-Management Officer
Company: Atrix Laboratories, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-482-5868	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Biostatistical Information Requests for NDA 21-794, ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Information requests for your new NDA 21-794, ACZONE™ (dapson topical gel) 5%, follow:

Biostatistics:

1. Please submit additional details regarding how the randomization was carried out in Studies DAP203 and DAP204 including what information was relayed to the third party and how the third party identified the appropriate randomization number. Please identify whether the randomization was done within centers or across centers and explain why there are many gaps in the randomization sequence (unused subject numbers) and why subject numbers were not always assigned in ascending order relative to the date of randomization.
2. Please submit additional details regarding whether small centers were pooled in the analyses in Studies DAP203 and DAP204. If the small centers were pooled for the analyses, please provide the list of centers that were combined.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT(ASCP), CDR
 Senior Regulatory Management Officer and IT Liaison
 DDDDP, ODEV, CDER
 U.S. Food and Drug Administration



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V**

FACSIMILE TRANSMITTAL SHEET

DATE: September 15, 2004

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: Atrix Laboratories, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-212-4950	Fax number: (301) 827-2075/2091
Phone number: 970-482-5868	Phone number: (301) 827-2063
Subject: Facsimile Transmission of Information Requests for NDA 21-794, ACZONE™ (dapson topical gel) 5%	

Total no. of pages including cover: 1

Document to be mailed: YES NO

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Document to be mailed: YES NO

Information requests for your new NDA 21-794, ACZONE™ (dapson topical gel) 5%, follow:

CMC:

Please provide the CFN or FEI # for all of the facilities listed as being responsible for the manufacturing, testing, and stability of the drug substance and drug product on Attachment 1 of Form 356h in Module 1, Volume 1 of NDA 21-794.

Biostatistics and General:

Please submit copies of all items previously submitted as MS Word XP files (i.e., protocols, Variables Tables, etc.) in pdf format.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT(ASCP), CDR
Senior Regulatory Management Officer
DDDDP, ODEV, CDER
U.S. Food and Drug Administration

Atrix Laboratories, Inc.
5% Dapsone Topical Gel (diaminodiphenylsulfone)
CTD Module 1 Administrative Information and Prescribing Information

1.3.5 FDA Form 3397 – Prescription Drug User Fee Cover Sheet

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG
USER FEE COVER SHEET**

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Atrix Laboratories, Inc.
2579 Midpoint Drive
Fort Collins, CO 80525-4417

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-794

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(970) 212-4901

3. PRODUCT NAME

5% Dapsone Topical Gel [Aczone™]

6. USER FEE I.D. NUMBER

4777

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

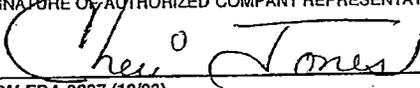
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Vice President, Regulatory Affairs

DATE

08/31/2004



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE V**

FACSIMILE TRANSMITTAL SHEET

DATE: May 5, 2004

To: Hansa Isokoski, Manager, Regulatory Affairs	From: Frank H. Cross, Jr., M.A., CDR Senior Regulatory Management Officer
Company: Atrix Laboratories, Inc.	Division of Division of Dermatologic & Dental Drug Products
Fax number: 970-482-9734	Fax number: (301) 827-2075/2091
Phone number: 970-212-4974	Phone number: (301) 827-2063

Subject: Facsimile Transmission of Pre-NDA Meeting Minutes for IND 54,440, Dapsone Topical Gel

Total no. of pages including cover: 15

Document to be mailed: YES NO

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Document to be mailed: YES NO

Please find attached to this facsimile transmission our Pre-NDA Meeting Minutes for your IND 54,440, Dapsone Topical Gel.

Please note that footnote # 5 on page 9 of the enclosed meeting minutes refers to the following citation:

National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard—Fifth Edition. NCCLS document M11-A5. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2001.

Please call me when you receive this facsimile transmission.

Thank you.

Sincerely,

Frank H. Cross, Jr., M.A., MT(ASCP), CDR
Senior Regulatory Management Officer
DDDDP, ODEV, CDER
U.S. Food and Drug Administration

Meeting Date: April 7, 2004
Meeting ID# 12512

Time: 1:00 p.m.

Location: S200A

IND 54,440, Dapsone Topical Gel

Topical Treatment of Acne vulgaris

Sponsor: Atrix Laboratories, Inc.

Pre-NDA Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Jonca Bull, Office Director, ODEV, HFD-105,
David Lin, Ph.D., Division Director, DNDCIII, HFD-830
Ernie Pappas, Chemistry Reviewer, DNDCIII, HFD-830
Norman See, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Tapash Ghosh, Ph.D., Biopharmaceutics Reviewer, DPEIII, HFD880
Ribhi Shawar, Ph.D., ABMM, Clinical Microbiology Reviewer, DAIDP, HFD-520
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alesh, Ph.D., Biostatistics Team Leader, DOBIII, HFD-725
Kathleen Fritsch, Ph.D., Biostatistician, DOBIII, HFD-725
Roy Blay, Ph.D., Director, Regulatory Review Officer, DSI, HFD-46
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

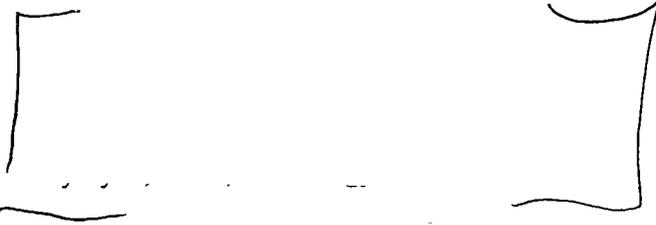
Atrix Laboratories, Inc.

J. Steven Garrett, D.D.S., M.S., Senior Vice President, Clinical Research
Cheri Jones, M.S., RAC, Vice President of Regulatory Affairs
Hansa Isokoski, M.S., (Pharm.), Manager, Regulatory Affairs
Craig Wesselman, Supervisor, Biostatistics
John McKenzie, M.S., DABT, Manager, Preclinical Pharmacology/Toxicology
Brent Coonts, B.S., Associate Director, Analytical Methods Development Services
Elyse Wolff, MT(ASCP), Director, Technical Affairs
Ken Godowski, M.T., M.S., Manager, Microbiology Laboratory
Alyssa Carter, M.A., Associate, Regulatory Affairs

Fujisawa HealthCare, Inc.:

Joyce Rico, M.D., Senior Medical Director, Research and Development
Jim Keirns, Ph.D., Sr. Director, Biopharmaceutical Sciences

Herm Lilja, Ph.D., Director, Toxicology, Biopharmaceutical Sciences
Rita Kristy, M.S., Manager, Biostatistics
Rochelle Maher, Director, Drug Development/Project Management
Donald Baker, J.D., Senior Director, Regulatory Affairs
Niten Barua, M.S., M.B.A., Associate Director, Regulatory Affairs and Quality
Paul Blahunka, Pharm.D., Fujisawa Healthcare, Inc.
Jean Rumsfield, Pharm.D., Fujisawa HealthCare, Inc.



Fred Reno, Ph.D, Atrix Toxicology Consultant

With reference to the January 23, 2004, Pre-NDA Meeting Request and January 23, 2004, Pre-NDA Meeting Briefing Package, the following discussion took place:

Chemistry, Manufacturing and Controls:

1. Under the Drug Substance and Drug Product Regulation Specification: "Does the Agency concur that the specifications of the drug substance, Dapsone, USP, and drug product, 5% Dapsone Topical Gel, are acceptable?"

Agency:

No.

- a. A microscopic visual examination should be included for the drug substance and finished product release specifications. This is to ensure that the drug substance does not contain any extraneous contaminants and the drug product does not contain any drug substance crystals or show phase separation.
- b. A particle specification should be included for the drug substance specification. If the drug substance is completely dissolved during drug product manufacturing then the specification is not necessary.
- c. The particle size specification for the finished product release specification is not acceptable because it does not contain an upper limit. Please include an acceptance criterion for the particle size upper limit. This is to ensure that there are no large particles present.

- d. The finished product release and stability specification is unacceptable because it contained limits of _____ % for Dapsone content instead of _____, the Agency's specification for finished products. A content uniformity acceptance criterion of _____%, per USP, is acceptable.
 - e. Under the test attribute "Related Substances" the terminology of "other" and "total" is not clear. We recommend using the terminology "Any unspecified impurity" and "Total impurities". In addition, please indicate whether there are any specified unidentified impurities to be included under the test attribute for " Related Substances"
2. Under the Stability Documentation: "Will the accelerated _____) and real time _____ stability studies as described in Table 3 be adequate to support storage conditions of 15-30° C and an expiration date of 24 months?"

Agency:

Yes, with certain limitations. The data package proposed for submission to the NDA is not adequate to support storage conditions of 15-30C. The data could support storage conditions of 20-25C (68-77F). The storage statement can also include a statement of "excursions permitted to 15-30C (59-86F).

The Sponsor will consider this recommendation.

Determination of the expiration dating period that is supported by the stability data package will be made after the submitted data are reviewed. The Sponsor should refer to the ICH Q1E step 4 guidance on Evaluation of Stability Data. The approaches in that guidance should be considered when proposing an expiration dating period. If the Sponsor would like to discuss this in more detail we can accommodate that request - please contact the Project Manager.

3. Under DGME- Novel Excipient: The Sponsor plans to include an open copy of the DMF _____ in Module 3.2.A.3 Novel Excipients [5% Dapsone Topical Gel] of the NDA. Is this acceptable to the Agency?"

Agency:

Yes. However, we note that the holder of DMF # _____ will update and re-activate the DMF for the DGME excipient prior to the NDA submission. The NDA should include a letter of authorization from _____ which is dated after the re-activation of the DMF. This DMF should include the manufacturing process and all technical information regarding the DGME excipient.

4. Additional CMC Comments:

During the End of Phase 2 Meeting that was held on December 18, 2000, additional CMC information was requested. However, this information was not adequately addressed in the IND Amendment dated March 9, 2001, as follows:

- a. A letter of authorization was included for DMF # _____ to reference their DMF. However, this DMF does not appear on CDER's internet list of active

DMFs. In addition, COMIS shows no annual updates or reviews other than an authorization letter. The Sponsor should provide the current status of this DMF. During the meeting the Sponsor stated that _____ is now the current manufacturer and DMF holder.

- b. The IND Amendment contained the UV absorbance spectra for Dapsone. However, the spectrum was recorded between _____ nm, instead of _____ nm. Please provide the UV absorption spectra of all of the individual components analyzed from _____ nm. The Sponsor will provide these data.
- c. Please provide the photostability of the drug product as per ICH Guidance Q1B, "Photostability".
- d. Please provide the report on the possible solid-state forms (i.e., polymorphs) in the drug substance as required by Q6A [ICH] Guidance.
- e. Please include in the NDA submission a table listing the manufacturing and testing sites. The information in the table should include the site name, actual address (not the corporate address), contact name and phone number of the contact person. In addition, please include a statement that all the manufacturing and testing sites are ready for inspection at the time of NDA submission.
- f. It appears that _____ (January 23, 2004, Pre-NDA Meeting Briefing Package, pg. 20) will be the drug substance manufacturer for the NDA. Please clarify if _____ is the currently holder of DMF _____
- g. Please include in the NDA submission a complete formulation history, including composition variants and the studies for which each formulation was used.

Pharmacology/Toxicology:

- 1. Sponsor's question 2.1.2.2 of January 23, 2004, Pre-NDA Meeting Briefing Package: "Male reproduction (Segment 1) study ATLS-183...The final study report will be available in the third quarter of 2004. Atrix intends to submit the final study report in the 120-day safety update. Is this acceptable to the Agency?"

Agency:

Yes.

- 2. Sponsor's question 2.2.1 of January 23, 2004, Pre-NDA Meeting Briefing Package: "Does the Agency concur that the clinical and nonclinical studies and the presented comparative data adequately support the NDA?"

Agency:

The adequacy of the database will be a review issue under the NDA. It is unclear at this time if the level of exposure obtained in chronic topical toxicology studies was sufficiently high to qualify the level observed in patients under conditions of maximum exposure.

3. Sponsor's question 2.4.1 of January 23, 2004, Pre-NDA Meeting Briefing Package: "The Sponsor believes that all required preclinical studies in support of the NDA submission are either ongoing or have been completed. Does the Agency concur that these studies are adequate to support the NDA?"

Agency:

It appears that the database may be deficient with regard to data, which describe the genetic toxicology of DGME. As mentioned during the End of Phase 2 Meeting, it is recommended that the NDA be supported by a battery of studies (conducted with DGME) similar to that discussed in the ICH S2B document. The genetic toxicology studies stated to be contained in DMF (_____ assay and a _____ assay) would not be adequate. Supplementation of the existing database through performance of an *in vivo* micronucleus study should suffice, provided the quality of the genetic toxicology studies in the DMF were deemed adequate. The adequacy of the database to support approval of a NDA will be a review issue under the NDA.

4. Sponsor's question 2.4.2 of January 23, 2004, Pre-NDA Meeting Briefing Package: "[Regarding safety pharmacology]...Atrix believes that adequate information is available to support the NDA. Does the Agency concur?"

Agency:

The adequacy of the database will be a review issue under the NDA.

Biopharmaceutics:

1. Atrix believes that the PK studies (DAP9903, DAP0110, DAP0114 and the ongoing drug-drug interaction study) support the NDA and the Agency's previous comments. Does the Agency concur?

Agency:

As far as the nature of studies required to be conducted to generate systemic exposure data following topical application of Dapsone Topical Gel, 5%, the Sponsor has fulfilled the requirements. However, the Agency requests that the Sponsor submit dapsone, metabolite (N-acetyl dapsone) and G-6-PD levels and CBC data from subset of patients identified as G-6-PD deficient in these PK studies.

2. Atrix is planning to submit the final study report of drug-drug interaction study in 120-day safety update. Is this acceptable to the Agency?

Agency:

That is acceptable. However, should the clinical pharmacology and biopharmaceutics review be closed before receiving the report, no statement based on the outcome of this study may be included in the label.

Clinical Microbiology:

1. Question 2.1.1 (Items not covered by CTD format – Microbiology Section) of January 23, 2004, Pre-NDA Meeting Briefing Package: “Nonclinical data related to microbiology will be presented in Module 2.6.2.2 Primary Pharmacodynamics, and the clinical microbiology data from the clinical study DAP9907 will be presented in Module 2.7.2.4 Special Studies (Clinical Microbiology).
In vitro Minimum Inhibitory Concentration (MIC) reports will be placed in Module 4.2.1.1 Primary Pharmacodynamics, and the clinical study DAP9907 will be presented in Module 5.3.4.1 Healthy Subject PD and PK/PD Study Reports. See Table 9 Preclinical Development Program for Dapsone and Dapsone Topical Gel for a list of Arix *in vitro* MIC reports and Table 14 Summary of Clinical Studies of 5% Dapsone Topical Gel for a brief description of the clinical study DAP9907.

Does the Agency concur with this placement?”

Agency:

- a. The Sponsor is advised that Module 2, Section 2.7, Clinical Summary, subsection 2.7.2.4 should contain only the summary report. Thus it contains the information used to justify the Clinical Microbiology information placed in the product package insert.

Please provide microbiology nonclinical and clinical study reports used in the construction of the summary information (provided in subsection 2.7.2.4 above) in Module 5 Clinical Study Reports, subsection 5.3.5.4 "Other Study Reports". All of the study reports used to construct the summary report presented in Section 2.7.2.4 should be cross-linked to the summary report.

- b. The Sponsor is advised to provide further details and explanation of the lack of effect on *Propionibacterium acnes* in clinical study DAP9907 (Title: A 10-week, Single Center, Single-Blind, Microbiological Study of 5% Dapsone Topical Gel and vehicle control in normal subjects). The objective of this study was to compare differences in the bacterial counts of *Propionibacterium* species following daily applications of either 5% Dapsone Topical Gel or vehicle control. The efficacy results show that 5% DTG reduced the *Propionibacterium* counts from baseline by 63-70% while the VC reduced the *Propionibacterium* counts from baseline by 54-78%.

Did the Sponsor assess the activity of Dapsone against isolates recovered from this study? The Sponsor is advised to provide susceptibility testing results on recent (within 5 years) *P. acne* isolates recovered from the patient population. A minimum of 25 isolates should be tested.

2. Question 2.4.1 (Preclinical Studies - Adequacy of preclinical studies) of January 23, 2004, Pre-NDA Meeting Briefing Package: “The Sponsor believes that all required preclinical studies in support of the NDA submission are either ongoing or have been completed (see Table 9 Preclinical Development

Program for Dapsone and Dapsone Topical Gel and Table 10 Preclinical Development Program for DGME (Diethylene Glycol Monoethyl Ether) in Section 4.1 Introduction for the listing of pre-clinical studies for dapsone and DGNE conducted by Atrix.”

Does the Agency concur that these studies are adequate to support the NDA?

Agency:

- a. In table 9 of the January 23, 2004 Briefing Package, the Sponsor provided a list of 4 different *in vitro* microbiological study reports. No reports or summaries of the findings from these studies are presented with this submission. However upon inquiring, the Sponsor provided four Clinical Microbiology study reports and as well as an overview summary of the findings. This information is contained in the Sponsor's correspondence dated March 12, 2004. Given the fact that there is no literature or other data regarding the *in vitro* activity of dapsone against *P. acnes*, these reports offer some information regarding this activity and the potential for synergism between dapsone and trimethoprim. However, the Agency considers that these reports offer little assurance of the quality of the data. This is largely because of the following main deficiencies:
 - i. Report dated October 29, 1999:
 - Standard NCCLS methods were not followed. Contrary to what is mentioned in the reports, MIC testing was not conducted using NCCLS standard methods for antimicrobial susceptibility testing of anaerobes and deviations from testing were not justified. For example:
 - The effect of four different media on MIC was investigated and Mueller Hinton broth was chosen. However, supplemented Brucella broth, the test medium recommended by NCCLS was not among the media used.
 - Known QC organisms and drugs were used to determine if MICs are within acceptable ranges, but these ranges cannot be applied unless testing was done with strict adherence to NCCLS standards. In addition, in some cases the lower-end of the range tested could not be used to determine acceptability of the data (e.g., when the QC range is — the lowest test concentration cannot be — because the test will not be able to conclusively determine if the results are within the acceptable limits).
 - Dapsone stock standard used in the testing was found to be improperly prepared. This invalidates the data.
 - ii. Report dated September 13, 2002:
 - This report contains no description of test conditions, media, source of isolates or other details of the methods used for susceptibility testing or culture and identification of organisms.

- There is a discrepancy in the number of isolates mentioned in the text and tables (25 in tables vs. 2 in the summary).

iii. Report dated September 26, 2003:

- MIC values were determined by various methods. As mentioned above for the other reports, Standard NCCLS methods were not followed.
- Analysis of MICs obtained by different methods cannot be compared and correlated simply by calculating population MIC90s for each test method. The Sponsor is advised to consider analyzing such data through regressions of MIC vs. MIC to better understand correlations and identify potential discrepancies.
- Additional comments:

Synergy and time kill studies

- The Sponsor is encouraged to use calculations of fractional inhibitory concentrations when analyzing data from synergy studies.
- The Sponsor is encouraged to tabulate data to show time, concentration (at what multiple of MIC) at which 1, 2, 3 log reduction is observed.
- Does the Sponsor have or is planning to conduct studies to monitor viable counts at longer exposure times (e.g., up to 8 or 24 hours)?

iv. Report dated September 26, 2003:

- This report offers some information and reasonable *in vitro* data to suggest that synergy can be demonstrated with certain combinations of Dapsone and trimethoprim. However, Mueller Hinton broth and agar were used instead of the recommended media and test conditions according to NCCLS standards for antimicrobial susceptibility testing of anaerobes.
- If QC was included as part of this study, there was no data provided for known QC organisms and drugs to determine if MICs were within acceptable ranges.
- In the conclusions section on synergy, the Sponsor mentions the following: "This data implies that a dapsone finished product containing 3% dapsone could possess markedly improved anti- *P. acnes* efficacy if _____, were part of the formulation"
- It is unclear to the Agency how the Sponsor intends to use the information obtained from these synergy studies. Although the *in vitro* data suggests that improved activity can be obtained by this combination, the final validation requires further testing to correlate actual measurement of each drug component at the site. If the Sponsor wishes to pursue this formulation for future clinical testing they are

advised to consider conducting further preclinical studies of drug measurement/efficacy studies to demonstrate that the a new formulation containing the suggested ratio of the two drugs offers the concentrations of both drugs at the site and to confirm the potential advantage seen in MIC synergy studies.

The Sponsor is advised that the Agency recognizes the methods of the National Committee for Clinical Laboratory Standards for generating susceptibility data. NCCLS-approved standard documents for testing *in vitro* susceptibilities of anaerobes to several antibacterial agents including the test drug should be followed when performing such microbiological studies.⁵ There is no need to provide details of methodology when data is obtained by referenced NCCLS methods. However, if susceptibility data is obtained by modification of the NCCLS methods, or by other methods, it is recommended that the Sponsor include a detailed description of the method, including the justification for the modification of the NCCLS method and the impact on susceptibility results.

Furthermore, the Sponsor is advised that two endpoint-determining susceptibility testing methods for anaerobic bacteria are described by NCCLS; The agar dilution and broth microdilution methods. Agar dilution remains the reference standard and is also the standard to which other methods have been compared. NCCLS current recommendations limit broth microdilution method to testing of *Bacteroides fragilis* group organisms and selected antibiotics at this time.

3. Additional Agency recommendation:

Draft label:

Under the Clinical Pharmacology Section the Sponsor included a subsection called _____ . The Sponsor is advised to refer back to the Clinical Microbiology comments which were provided at the End of Phase 2 meeting (Facsimile transmission of May 11, 2001) where the Sponsor was informed to include a Clinical Microbiology heading and to include information such as *in vitro* activity and mechanism of action under this subheading.

4. During the meeting, the Sponsor discussed the possible wording of the label claims regarding the *in vitro* activity of dapsone against _____. The Sponsor presented two possible labeling wording both of _____ and that the clinical relevance of this activity is unknown. The Sponsor asked if literature data can be used to support the specified claim.

Agency:

The Agency reiterated that limited literature data with limited access to primary data make it difficult to assess the activity of dapsone against _____ without well controlled studies and current data. If the Sponsor ultimately wishes to include clinical relevance, data will need to be provided regarding pharmacokinetic and pharmacodynamics of the activity of dapsone in relationship to effects on _____ .

Action Item:

The Agency will discuss this issue internally and shortly get back to the Sponsor.

Addendum:

As previously mentioned during the pre-NDA meeting, the in vitro study reports which were submitted offer some information regarding this activity and the potential for synergism between dapsone and trimethoprim. However, these reports offer little assurance of the quality of the data. If the Sponsor wishes to include a wording in the label indicating _____, evidence in the form of primary data obtained from well controlled studies should be submitted for Agency review at the time of the original NDA submission. Data should be from studies conducted on recent clinical isolates and in accordance with anaerobic susceptibility test methods recommended by the National Committee for Clinical Laboratory Standards. Literature data, if available in the form of peer-reviewed journal articles and summaries are also acceptable as supportive information.

As previously mentioned during the pre-NDA Meeting, if the Sponsor desires to include in the labeling a claim regarding _____ evidence in the form of primary data obtained from well controlled studies should be submitted for Agency review at the time of the original NDA submission.

Clinical:

1. Clinical Question 2.5.1 (Clinical Studies) of January 23, 2004, Pre-NDA Meeting Briefing Package: "A listing of clinical studies completed to date is found in Table 12 Summary of Clinical Studies of 5% Dapsone Gel in Section 5.1 Introduction. Does the Agency concur that these studies are adequate to support the NDA?"

Agency:

Based on Section 5.0, Table 14 Summary of Clinical Studies of 5% Dapsone Gel (pages 62 – 70 of the January 23, 2004, Pre-NDA Meeting Briefing Package), the Sponsor has conducted studies recommended by the Agency to support filing of the NDA application; however, adequacy of the data for NDA approval is a review issue.

2. Clinical Question 2.5.1 (Case Report Forms) of January 23, 2004, Pre-NDA Meeting Briefing Package: "Atrix will submit copies of case report forms from the two pivotal studies DAP0203 and DAP0204, and long-term safety study DAP0114 for patients that discontinue the study due to adverse events and patients with Serious Adverse Events (Note: No deaths were reported in any clinical study). Are any other case report forms required in the initial submission?"

Agency:

Please submit CRFs for all patients who are excluded from per protocol analysis, who are lost to follow-up, or who are early discontinuations. Additional CRFs may be requested during the course of the review process.

3. Additional Agency Comments:
 - a. All available safety data should be submitted in the NDA.

- b. The Sponsor plans to present AEs for Glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients versus not deficient patients (pg. 199 of January 23, 2004, Pre-NDA Meeting Briefing Package) for studies that tested for G-6-PD. The Sponsor should provide PK data analysis correlating dapson levels, G-6-PD deficient patients, and CBC results after significant period of topical dapson use. The Sponsor might also supplement with literature in regards to lowest systemic levels of dapson and hemolysis. The Sponsor should address the risk for patients using dapson gel on a chronic basis to develop anemia.
- c. Please include in the submission an index that would enable the reviewer to make the association between investigator's verbatim terminology used to describe an adverse event and the preferred term used for coding the adverse event in the submission's adverse event tables.
- d. Please generate a table showing all lab parameters for patients with SAEs and discontinuations.
- e. Please provide electronic copies text assessable files for the following sections of the application would greatly facilitate the review process:
 - i. Integrated Summary of Efficacy
 - ii. Integrated Summary of Safety
 - iii. Clinical study reports for the pivotal trials
 - iv. Protocols and amendments for the pivotal trials
 - v. Draft package insert and patient information insert
 - vi. In the course of the review, electronic copies of other sections of the application may be helpful to the reviewer.
- f. Please provide desk copy sets for the clinical reviewer and team leader.
- g. Please include in the submission the primary efficacy analysis broken down by investigator.
- h. It appears that the benefit of this product, dapson gel, is marginal versus its vehicle comparator for treatment of acne vulgaris. This will need to be balanced with the risk of using this topical product in the Agency's decision process.

Biostatistics:

1. Biostatistics Question 2.6.1 (ISE and ISS) of January 23, 2004, Pre-NDA Meeting Briefing Package: "Does the Agency concur with the planned analysis of the ISE and ISS, located in Summary of Clinical Efficacy and 5.2.2 Summary of Clinical Safety and Tabs E and F? See also Question 2.1.1 Items not Covered by the CTD Format."

Agency:

The plans for the ISE appear to be acceptable. The Sponsor is referred to the guidance Format and Content of the Clinical and Statistical Sections of an Application: (www.fda.gov/cder/guidance/statnda.pdf) for further information on the contents of the ISE.

2. Biostatistics Question 2.6.2 (SAS Transport Datasets) of January 23, 2004, Pre-NDA Meeting Briefing Package: "Atrix intends to submit SAS transport datasets for the following studies: DAP0203, DAP0204, and DAP0114. Atrix will also submit pooled datasets of the ISE and ISS in SAS transport format files. Is this adequate?"

Agency:

In addition to the above studies, please submit the SAS transport dataset for Study DAP0004.

The submitted database for the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses (such as percent reduction in lesions, success on the global acne assessment score, and indicators for ITT, MITT, and PP status). The submission should include adequate documentation for the datasets including definitions, formulas for derived variables, and decodes for any classification variables.

3. Biostatistics Question 2.6.3 (Success of the Pivotal Studies) of January 23, 2004, Pre-NDA Meeting Briefing Package: "In the End-of-Phase 2 meeting minutes the Agency states that the Sponsor will "win" if, at the end of the study, they win on two of the three sets of lesion counts (mean percent reduction from baseline for inflammatory, non-inflammatory, and total lesions), plus the investigator's global assessment of acne (See Tab C for the FDA communication dated January 25, 2001/Biostatistics Comment 1, Page 8). The same comment on success was repeated during the Special Protocol Assessment of the two pivotal studies DAP0203 and DAP0204 (See Tab C for the FDA communication dated August 5, 2002, Clinical Comment 6, Page 2). In the two pivotal studies DAP0203 and DAP0204, 5% DTG is superior to VC in the three lesion count categories as well as the Global Acne Assessment for the Intent-to-Treat (ITT), Modified Intent-to-Treat (MITT) and Per-Protocol (PP) patient populations. Therefore, Atrix believes that the Agency's requirement for success has been met for both pivotal studies. Does the Agency agree?"

Agency:

The Phase 3 studies appear to be adequate for filing, and would be reviewed in line with the agreements reached through the End of Phase 2 meeting and the Special Protocol Assessment.

4. Additional Agency Comments:

The NDA submission should include the following items:

- a. study protocols, any protocol amendments, and statistical analysis plans

- b. the randomization lists and the actual treatment allocations (with date of randomization) from the trials.

Project Management:

1. At the time of submission of the NDA, DSI will discuss the need for clinical site inspections with the clinical and biostatistical reviewers. If there is a need for inspection of clinical sites, DSI will contact the Sponsor's regulatory representative to discuss relevant data issues.
2. Regarding the Sponsor's CTD format for the proposed NDA, the ISS and ISE should go under 5.3.5.3
3. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
4. For applications submitted after February 2, 1999, the Applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
5. All manufacturing facilities named in your proposed NDA should be ready for inspection when the application is submitted. We recommend that this information be provided in the application in the form of a table or spread sheet so that these sites can be properly identified early in the review process.
6. We understand from your pre-NDA Briefing Package that the proposed timing of your NDA submission is for the third quarter 2004.
7. The Agency's comments in this document pertain only to the Sponsor's plan to submit the proposed NDA as a paper submission.

The meeting ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Jonathan Wilkin
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/s/

Frank Cross
5/5/04 01:46:37 PM .
Faxed to Sponsor on 5/5/04.

Meeting Date: December 18, 2000
Meeting ID# 6354

Time: 1430

Location: N225

IND 54,440, Dapsone Topical Gel

Topical Treatment of Acne vulgaris

Sponsor: Atrix Laboratories, Inc.

End of Phase 2 Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonca Bull, M.D., Deputy Office Director, ODEV, HFD-105
Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Norman See, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Susan Walker, M.D., Dermatology Team Leader, DDDDP, HFD-540
Steve Thomson, Biostatistician, DOBIII, HFD-725
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

David Osborne, Ph.D., Vice President of Pharmaceutical Development
Steve Garrett, D.D.S., Vice President of Clinical Research
Fred Reno, Ph.D, Toxicology Consultant
Kathleen Holland, D.V.M., Preclinical Section Head
Joanna Peterkin, M.D., Medical Consultant
Graham Carron, M.S., Biostatistics Supervisor
Elaine Gazdeck, R.A.C., Vice President of Regulatory Affairs/Quality Assurance
Amy Taylor, Regulatory Affairs Manager
Robert Nelson, Regulatory Affairs Associate

With reference to the November 14, 2000, End of Phase 2 Meeting Briefing Package, the following discussion took place:

Agency:

Chemistry, Manufacturing and Controls (CMC):

1. Question 1, Section 2.3, of November 14, 2000, End of Phase 2 Meeting Briefing Package, "Is the proposed stability protocol acceptable to establish the primary stability for the drug product?"

Agency:

No. The proposed protocol does not follow the usual time points between intervals. In order to support a one-month expiry, the time points should be at 0, 3, 6, 9, 12, 18, 24 and 25 months (i.e., an experimental point at expiry). If the 25-month time-point is a typographical error, it should be corrected wherever it appears. We recommend that the ICH guideline of at least 12 months of long-term stability data at the time of the NDA submission should be followed.

2. Additional CMC comments.

- a. The Sponsor should monitor for other solid-state forms (i.e., polymorphs) in the drug substance.
- b. The drug substance manufacturer, _____, should be asked to provide a letter authorizing reference to their DMF. The data submitted at Tab F appears to be from the "open" section of this DMF.
- c. The Sponsor is proposing to monitor particle size in the drug product; the results of these measurements should be included in stability reports. We also note the description of the product as a _____ (tab B, pg. B4); this description may not be acceptable. The Sponsor is referred to ICH Q6A Specifications: "Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances."
- d. The UV absorbance spectrum of dapson is described at tab F, page F17. However, the accompanying enclosures do not have a scale on the abscissa to show the wavelength. This information should be resubmitted, and should include the range from _____ nm. The UV absorption spectra analytical wavelength of all the individual components should be analyzed from _____ nm. The UV absorption spectra of all the individual components should be analyzed from _____ nm which concerns photosensitization, photostability and phototoxicity.
- e. The Sponsor is advised to consider the photostability of the drug product and is referred to the ICH Guidance Q1B, "Photostability Testing."
- f. DMF references should be provided for the packaging components. Letters of Authorization to Cross-Reference the DMFs should also be provided.

Pharmacology/Toxicology:

1. Nonclinical Question 1, Section 2.2, November 14, 2000, End of Phase 2 Meeting Briefing Package: "The Sponsor believes all preclinical studies required for initiation of phase 3 have been completed, and that all additional preclinical studies required for filing are either in-progress or planned. Does the agency concur?"

Agency:

It appears that the nonclinical database will adequately support initiation of the proposed Phase 3 studies.

When available, please submit data which compare the systemic exposure (AUC) achieved in patients (under conditions of maximum exposure within the context of the anticipated label of the product) with the systemic exposures achieved in animals in the pivotal nonclinical studies. The exposure data should include any major metabolites (in addition to the parent compound). The clinical exposure data should be derived from studies approved by the biopharmaceutics and clinical reviewers, but the goal should be to measure systemic exposure under steady-state conditions of use in patients with representative acne who twice daily apply the product to the maximum body surface area over which the product may reasonably be used post-approval (i.e., face, neck, shoulders, back, chest, etc.). The Agency has been awaiting submission of appropriate comparative pharmacokinetic data (based upon conditions of maximum clinical exposure) prior to deciding whether or not data from repeat-dose oral toxicology studies in a nonrodent species would be necessary. If toxicokinetic data from the chronic topical dermal toxicology study being conducted in rabbits demonstrate that animals in that study experienced an adequate level of systemic exposure relative to systemic exposure observed clinically under maximum conditions of use (e.g., a rabbit:human AUC ratio of at least 5), then it may not be necessary to conduct repeat-dose oral toxicology studies in nonrodents. However, if the Sponsor does not wish to wait for the clinical exposure data to become available, then appropriate animal studies involving oral administration may be initiated to ensure that the data will be available if needed. A properly designed 90-day oral toxicology study in rabbits or dogs would probably suffice, provided data from that study did not indicate the need to obtain data over a longer time frame. In addition, as a filing issue, a NDA should be supported by data which fully describe the genetic toxicology of DGME; a battery of studies similar to that described in the ICH S2B document is recommended.

2. Nonclinical Question 2, Section 2.2, November 14, 2000, End of Phase 2 Meeting Briefing Package: "In the male rat fertility study dosage dependent reductions in sperm motility, sperm count, and number of implantations was observed at [all dapsones dosages studied]. A study designed to find the no-observable-adverse-effect-level in male rats is planned. Does the agency agree that this study is necessary?"

Agency:

Yes. When the data are submitted, please be sure to include a discussion which directly compares the systemic exposure levels (AUC values) for the no-effect level and the lowest level demonstrated to have an effect with the clinical systemic exposure level (under conditions of maximum exposure, as described above).

3. Nonclinical Question 3, Section 2.2, November 14, 2000, End of Phase 2 Meeting Briefing Package: "The Sponsor requests the agency's concurrence that the final report for the rat carcinogenicity study can be submitted after the approval of the NDA."

Agency:

The Agency does not concur. The carcinogenicity data will be needed to assess the safety of the product.

Inclusion of the final report of the two-year rat bioassay in the initial submission to a NDA will be regarded as a filing issue. It will be a review issue to determine if the proposed use of the product is associated with a risk-benefit assessment that favors chronic use of the product in a young, healthy patient population.

Sponsor:

The Sponsor will submit their proposed Tg.AC protocol to the Agency for review and comment.

Biopharmaceutics:

Currently the Sponsor has conducted an in vivo biostudy in patients with acne vulgaris of the face. As is our standard for all topical therapies we attempt to obtain maximal exposure data by using maximal doses over the widest feasible surface area consistent with the disease. As acne is also a disease of the back and chest we cannot accept this study as a maximal use study. A new study, using a similar design should be initiated in patients with acne vulgaris toward the upper range of the proposed disease severity scale consistent with their indication. A sufficient numbers of subjects should be studied so that reasonable and adequate pk parameter determinations can be made. Based on their previous study of facial acne, a total of 12 - 24 subjects should be sufficient for this type of trial based on the observed variability from their DAP-003 trial. In regards to the duration of the trial, as the maximum observed concentration occurred at day 7, a 14 day trial, rather than the 28 day protocol used in their current study would be sufficient.

An issue has been raised regarding the systemic exposure and subsequent safety of transcutool. In order to properly assess this, the sponsor is requested to modify their pk sampling strategy to allow for the assessment of transcutool plasma levels. Because of the initial exploratory nature of this issue, the sponsor may employ a surveillance type sampling strategy for transcutool whereby a reduced sampling strategy is employed. In any event, the sponsor is strongly encouraged to submit this protocol with changes for FDA review and concurrence prior to study initiation.

Clinical:

1. Clinical Question 1, Section 2.1, November 14, 2000, End of Phase 2 Meeting Briefing Package: "Design of the Phase 3 study specifies twice a day application of Topical Dapsone Gel to the face. Does this treatment protocol support the label indication "Dapsone Topical Gel is indicated for the topical treatment of acne vulgaris"?"

Agency:

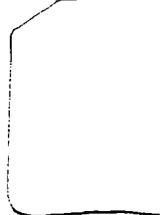
Twice daily application would support the indication "for the topical treatment of acne vulgaris". The sponsor is reminded that two adequate and well controlled trials are necessary to support the indication.

Protocol DAP0004 (in briefing packet Tab B, pg. B5 of B37 dated 14 Nov 2000) is a multicenter, double-blind, randomized, parallel-design study of the effects of twice daily applications of 5% formulation Dapsone Topical Gel or vehicle control when administered for 12 weeks to patients with moderate to moderately severe acne vulgaris. The number of applications needed to establish efficacy should ideally be determined during Phase 2 dose ranging studies.

2. Clinical Question 2, Section 2.1, November 14, 2000, End of Phase 2 Meeting Briefing Package: "Does the proposed patient population for the Phase 3 clinical study support the indication statement and dosage administration instructions?"

(Tentative Drug Product Labeling, [pg. 23 of 66, Indications and Usage] and [pg. 26 of 66, Dosage and Administration]) are listed as follows:

Indications and Usage:



Agency (Study schematic page B23):

- a. Proposed number of subjects on study medication is only 159. Sponsor is referred to the ICH (e) (1) (a) document. Sponsor should present rationale for potential exclusion of female patients from the clinical trials (Page B8, inclusion criteria 3 and 4). Study design in phase 3 may have labeling implications for marketing.
- b. Acne endpoints recommended by the Division are reduction in lesion counts and the investigator's global assessment.
 - i. Baseline and Endpoint lesion counts should be presented for non-inflammatory lesions, inflammatory lesions, and total lesions. Two out of these three should demonstrate superiority to vehicle.
 - ii. The investigator's global assessment scoring at Endpoint should be based upon a clearly defined static scoring scale with discrete descriptions for each level. Levels of the global assessment should be dichotomized to success/failure for efficacy evaluation.
 - iii. Superiority to vehicle in two of the three measures of lesion count reduction PLUS superiority to the vehicle in the investigator's global assessment should be demonstrated.
- c. For moderate facial acne, a minimum of 20 comedones and a minimum of 20 inflammatory lesions are recommended at baseline. No nodules should be present. (Criterion # 8 states that patients must have a clear diagnosis of moderate to moderately severe acne vulgaris of the face, as defined by having 15 inflammatory acne lesions (pustules and papules), 10 comedones, and 3 nodules above the mandibular line at Baseline).
- d. The Sponsor has an extensive exclusion criteria list. Exclusion criteria ultimately may be reflected in the label.

An attempt should be made to conduct the Phase 3 study in a population that mirrors the US population with acne vulgaris that is expected to use the product post approval. The sponsor should re-assess exclusion criteria and limit exclusion to data driven safety concerns.

- e. Washout periods should reflect the pharmacology of the drug. Traditionally, the following washout periods have been suggested:
 - Topical acne treatment - 4 weeks
 - Topical or systemic corticosteroids - 4 weeks
 - Topical or systemic anti-inflammatories - 4 weeks
 - Topical or systemic antibiotics - 4 weeks
 - Systemic retinoids - 3 months
 - f. The recommended lower pediatric age is 12 years of age.
 - g. Specific monitoring for local adverse events (e.g., erythema, burning, peeling, etc.) should be performed and graded.
 - h. Test article accountability should include return and weighing of test drug materials at each visit to determine actual extent of use. (page B7)
 - i. The protocol should very clearly state the method of application of the drug product, as this information should be included in labeling. i.e. directions for use on page B12 recommend "_____ cleanser". It may be more appropriate to specify a soapless cleanser instead of a specific item.
 - j. Sponsor should consider that addition of instructions to the investigator for instances of inadvertent ingestion of the drug during the trial (see p26 of proposed package insert)
3. Clinical Question 3, Section 2.1, November 14, 2000, End of Phase 2 Meeting Briefing Package: "Is the Modified Cook Scale an appropriate instrument for assessing "global" acne improvement in a Phase 3 clinical program? (See Tab B, appendix F of the clinical study protocol for Modified Cook Scale)."

Agency:

For assessing "global" acne improvement, the scale provided is static and does not provide discrete descriptions for each level; however, a four-point ordinal scoring scale is recommended. Global assessments should be dichotomized to success/failure for efficacy evaluation.

4. Clinical Question 4, Section 2.1, November 14, 2000, End of Phase 2 Meeting Briefing Package: "Will the Agency grant a partial waiver for pediatric use to Atrix for the requirements set forth in 21 CFR § 314.55 (a) based on the information provided in Section 4.1?"

Agency:

(Pg. 15 of 66, Section 4.1, Pediatric Use Information) A partial waiver in accordance with 21 CFR § 314.55 should be requested by the sponsor for pediatric patients under 12 years of age since the incidence of acne vulgaris is low in this age group.

5. Additional Comments:

a. Topical Safety Studies:

i. The Sponsor should note that all of these studies should be conducted with the final "**to-be-marketed formulation**". Topical Safety Studies recommended by the Division are:

- Cumulative irritancy (50 subjects needed)
- Contact sensitization (200 subjects needed)
- Phototoxicity (25-30 subjects needed)*
- Photocontact allergy (30 - 50 subjects needed)*

***Note:** If the Sponsor can demonstrate that there is no absorption for any component of the product in the UVB/UVA/visible spectrum (nm), a waiver for phototoxic and photocontact allergic potential studies should be requested.

b. Additional comments

- i. Treatment with systemic dapsone has the inherent potential for severe and life threatening adverse events. Its use is generally limited to relatively severe clinical conditions and accompanied by close hematologic monitoring. The Sponsor's submission should very clearly delineate the risk/benefit assessment for treatment of facial acne with dapsone, by providing adequate data to demonstrate that the inherent risk for serious side effects is vanishingly small.
- ii. 12 weeks is the traditional clinical efficacy endpoint for acne products. As most topical medications have not been demonstrated to have adverse systemic effects, usage beyond 12 weeks has not been a significant safety issue. However, dapsone is known to cause hematologic abnormalities. The sponsor should demonstrate that chronic topical use of dapsone does not place the patient at risk for any of the known dapsone side effects. Consult ICH (e) (1) (a) document.
- iii. The current briefing package indicates that there is only one component of the drug product (dapsone) which contributes to the efficacy of the drug product. If the sponsor intends to pursue a marketing claim for any component of the product other than the ingredient "dapsone", then a different clinical trial design (i.e. combination product) would be appropriate. (see page B4, paragraph 3).

Sponsor:

The Sponsor said that there is no intent for such wording in labeling and/or advertisements.

Agency:

- iv. The Sponsor should submit their Phase 3 protocols to the IND for review and comment prior to study implementation. These final protocols should be marked with HIGHLIGHT and STRIKEOUT to elucidate ANY CHANGES from the versions of the protocols submitted for review for today's meeting.
- c. Comments on Package Insert (page 22):
- i. Information included under "mechanism of action" should be supported by adequate data. Consider consolidating all potential systemic sequelae into one section.
 - ii. Sponsor should provide rationale for including contraindications section as presented on p23/24. Cautions for use of dapsone gel (p24) would assume that the product has significant clinical absorption.
 - iii. Sponsor should pursue adequate clinical trials prior to approval in order to determine whether or not drug interactions are a potential hazard with use of topical dapsone.
 - iv. Sponsor should justify the inclusion of warnings for oral dapsone in the label for the topical product(adverse reactions section).
 - v. Package insert should include a clinical trials section
 - vi. Package insert should include an adverse reactions section which describes the local adverse events occurring in the trial.
 - vii. Please refer to 21 CFR 201.57, Content and Format for Labeling.

Biostatistics:

These comments apply to the draft protocol DAP0004: A 12 week, Multi-center, Double-blind, Randomized, Parallel-Design Study of Dapsone TopicalGel and Vehicle Control in Patients with Acne Vulgaris.

- 1. Note that, as indicated by the Medical Officer, all three sets of lesions: inflammatory lesions, non-inflammatory lesions (i.e., comedones), and total lesions should be analyzed, using both absolute lesion counts and percentage change from baseline. The Sponsor will "win" if, at the end of the study, they win on two of the three sets of lesion counts, plus the investigator's global assessment of acne. Note if the claim is based on multiple time points there will need to be an adjustment for multiplicity. As discussed by the Medical Officer, for the analysis, the global assessment should be reduced to a binary "success-fail" scale for analysis.
- 2. The Sponsor should redo the power calculations on page 3 of the protocol for the primary endpoint proposed in the first bullet above. This should use the maximum of the sample sizes for the physician's global

evaluation, and the analyses of both total lesions and percent change from baseline for the chosen lesion counts (presumably inflammatory lesions and total lesions).

3. The Sponsor proposes to randomize up to 318 patients in 15 centers with a maximum of 35 patients per center. We would recommend an allocation of patients so that there are at least 9-10 subjects per treatment arm per center.
4. The Sponsor does not define appropriate populations to be analyzed. The Sponsor defines the primary analysis as the difference between the mean week 12 total inflammatory lesions in each treatment group. Following the ICH E9 guidelines the recommended population group for superiority trials is the ITT population, usually defined as all subjects randomized and dispensed medication, not the 12 week completers. This analysis is usually implemented using last-observation-carried-forward (LOCF) technology at the end of the study.
5. Further, the Sponsor suggests that "additional independent variables may include factors such as the initial lesion count." Factors and covariates to be used in the analysis should be both very limited in number and pre-specified in the protocol. Use all prespecified covariates in the analysis.
6. For these lesion counts the Sponsor states that "In the event that the assumption of normality is not satisfied, and appropriate nonparametric method (e.g., Wilcoxon Rank Sum test) may be used." This seems to ignore the inherent robustness of ANOVA, particularly if the data are not too unbalanced. However, any such nonparametric test should be stratified on center, and the exact test to be used should be pre-specified, not left to a choice of "appropriate nonparametric method."
7. Also, as noted by the Medical Officer, for efficacy and safety claims usually two well controlled trials are needed.

Project Management:

1. Pediatric Rule:

The Sponsor was reminded of the following:

The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

Waivers are requested in accordance with 21CFR 314.55(c)

2. Financial Disclosure:

For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

3. Labeling:

If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the NDA.

4. Please submit the proposed annotated labeling and unannotated labeling with the NDA. A copy of the proposed labeling on diskette in MS Word should also be submitted with the NDA.

Action Item:

The Sponsor will submit a TgAC protocol to the Agency for its review.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

cc:

Orig IND 54,440
HFD-540
HFD-105/OFFICE DIR/DeLap
HFD-105/DEP OFFICE DIR/Bull
HFD-540/DIV DIR/Wilkin
HFD-830/DIV DIR/Chen
HFD-830/DEP DIV DIR/Dunn
HFD-540/CHEM TL/DeCamp/12.18.00
HFD-540/CHEM/Timmer
HFD-540/PHARM-TOX TL/Jacobs
HFD-540/PHARM-TOX/See/12.18.00
HFD-880/BIOPHARM TL/Bashaw/12.22.00
HFD-520/CLIN MICRO TL/Sheldon
HFD-520/MICRO/Altaie
HFD-540/DERM TL/Walker/12.18.00
HFD-540/MO/Vaughan
HBFD-725/BIOSTAT TL/Alosh
HFD-725/BIOSTAT/Thomson/12.18.00
HFD-540/PROJ MGR/Cross
Drafted by: fhc/December 18, 2000
d:\word\dapsone\ind54440\eop2min.doc

MEMORANDUM OF MEETING

/s/

Frank Cross

1/25/01 12:55:07 PM

CSO

Finalized End of Phase 2 Meeting Minutes faxed to Sponsor on 1/25/01.

N/A