CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-794

CHEMISTRY REVIEW(S)

NDA 21-794

ACZONE(dapsone) Gel, 5 %

QLT USA , Inc.

Ernest G. Pappas
Division of Dermatological and Dental Drug Products

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APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA # 21-794

2. REVIEW #: 1

3. REVIEW DATE: 6/30/05

4. REVIEWER: Ernest G. Pappas

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	8/31/04
Amendment	9/15/04
Amendment	4/7/05
Amendment	4/22/05
Amendment	6/03/05
Amendment	6/08/05
Amendment	6/20/05
Amendment	6/30/05

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: QLT USA, Inc.

Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417

Representative: Cheri Jones

Telephone: 970-212-4901

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Aczone
b) Non-Proprietary Name Dapsone (USAN):
c) Code Name/# + DAPE
d) Chem. Type/Submission Priority (ONDC only):

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

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

10. PHARMACOL. CATEGORY: Topical treatment of acne vulgaris

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 5%

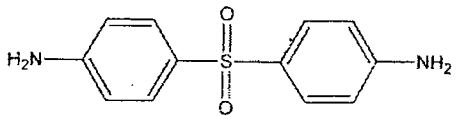
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: x Rx ___OTC

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

___X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 248.30



Molecular formula: $C_{12}H_{12}N_2O_2S$

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Dapsone	3	Adequate	3/11/04	IR drafted 5/18/05
	IV			7	Adequate		Never reviewed; USP Grade; Actively used as an excipient in the USA as a cosmetic formulations.
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	6/15/05	Adams
DMETS	Acceptable	2/28/05	Holquest
Microbiology	Acceptable	3/11/05	Riley

APPEARS THIS WAY
ON ORIGINAL

The excipients of Dapsone Gel are commonly used in formulations and do not impact on the safety from CMC standpoint. These excipients, with the exception of carbomer 980 are USP/NF monographs and must comply with the acceptance criteria as stipulated in the monographs. Since Carbomer 980 is equivalent to Carbomer 940, NF, it also must comply with the acceptance criteria as indicated in the monograph for Carbomer 940, NF.

Dapsone Gel is a suspension of dapsone drug substance [redacted] Carbomer 980 is the [redacted] This suspension consists of dapsone particles dispersed throughout [redacted]. Analytical data submitted for several lots of drug product also show that [redacted] of the total DS also remain soluble in the vehicle.

A critical manufacturing parameter for the 5% Dapsone Gel is the [redacted]

The particle size distribution was evaluated on the clinical supplies and primary stability lots manufactured from the commercial 5% Dapsone Gel formulation. The results of particle size testing of 10 lots of 5% Dapsone Gel demonstrate that the product maintains a consistent particle size distribution throughout the proposed shelf life of 24 months. From the dataset it was demonstrated that majority of the particles remained below [redacted] microns. The particle size distribution data show that NLT [redacted]% of the particles are less than (LT) [redacted] microns, with the largest individual particle that measured at [redacted] microns. Therefore, an acceptance criteria was established for the drug product at NLT [redacted] % of the particles are LT [redacted] microns, NLT [redacted]% of the particles are LT [redacted] microns, and NLT [redacted] % of the particles are LT [redacted] microns, with the maximum particle size NMT than [redacted] microns. It was also demonstrated from the data that the drug substance crystals have [redacted] form.

Although, one would think that the Applicant may have used some alternate manufacturing procedure where the drug substance particle size could have been controlled to manufacture product with much finer suspended particles rather than letting [redacted], these proposed acceptance criteria for the particle size distribution along with manufacturing step controls will ensure that all the future commercial batches will be similar to the clinical batches.

The drug product regulatory release and stability specification contains the acceptance criteria for testing 5% Dapsone Gel. These specifications were reviewed and found acceptable. The assay of dapsone content and control of the particle size distribution in 5% Dapsone Gel ensures batch-to-batch reproducibility of future commercial lots.

Stability data were submitted on three primary batches of the 5% Dapsone Gel as packaged in the container/closure system proposed for the marketed product (3 g and 30 g sizes). I ——— of room temperature data were submitted in support of the proposed 24 month expiration date. The stability data were found acceptable to support an expiration date of 24 months.

The labeling was reviewed and found acceptable from a technical standpoint with exception of minor revisions. The proprietary name Aczone has been reviewed by DMETS and DDMAC found acceptable for naming the 5% Dapsone Gel. The storage condition, "Store at controlled room temperature 20 ^{0}-25 ^{0}C (68 ^{0}F-76 ^{0}F) has been recommended on the packaging labeling. It is also recommended to "Protect from freezing and light. Return to original carton after application".

Establishment Inspections: All facilities as indicated in the NDA are found acceptable for CGMPs. An overall recommendation of "acceptable" was received from the Office of Compliance on 6/14/05.

Environmental Assessment: The applicant's claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable since the EIC projection was found to be at a level well below 1 ppb.

(2) Drug Substance:

Dapsone is the drug substance used in the proposed formulation for Aczone Gel, 5 %. This drug substance is also used in the marketed product, Dapsone Oral Tablet, 25 mg and 100 mg (ANDA 86841). Dapsone drug substance is the subject of DMF ——— ——————— This DMF was reviewed and found acceptable (see Chemist's Review dated 6/16/05). The DMF and subject NDA contained regulatory specifications for release of Dapsone drug substance to ensure its identity, strength, quality and purity that it purports to possess. The assay results were found to fall within the acceptance criteria. The structure and physicochemical characteristics are adequately described in DMF and NDA, including sophisticated methodology in the characterization of Dapsone drug substance. No isomers have been identified for ——— material.

Dapsone, USP is a white crystalline powder that is very slightly soluble in water and soluble in organic solvents. Dapsone has ——————————

Two impurities have been identified by the drug substance manufacturer, [redacted]. These impurities were addressed in DMF [redacted] and found acceptable (see Chemist Review dated 2/25/05). These impurities are [redacted] and listed as related impurities under the regulatory specification for Dapsone. The acceptance criteria for these impurities were found to be acceptable.

The stability data were reviewed for five lots. These data were reviewed and found acceptable. Based on the evaluation of the primary stability data, the proposed retest date of 24 months was deemed acceptable.

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

Treatment of acne vulgaris. Apply a thin layer of the drug product to the affected skin once daily.

C. Basis for Approvability or Not-Approval Recommendation N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

81 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Ernest G. Pappas
7/1/05 09:10:17 AM
CHEMIST
My chemistry ready for signature. Recommend approval of NDA from a chemistry perspective.

Ramesh Sood
7/1/05 09:12:34 AM
CHEMIST