IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kevin S. Warner *et al.*	Group Art Unit: 1629
Serial No.: 14/082,955	Examiner: Leslie A Royds Draper
Filed: November 18, 2013	Confirmation No.: 1222
For: TOPICAL DAPSONE AND DAPSONE/ADAPALENE COMPOSITIONS AND METHODS FOR USE THEREOF	FILED ELECTRONICALLY

DECLARATION OF KEVIN S. WARNER, PH.D. UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Kevin S. Warner, Ph.D., hereby declare:

1. I am a co-inventor in the above-captioned patent application.

2. I am an employee of the Applicant, Allergan, Inc. I have a Bachelor's of Science in chemistry from Brigham Young University and a Ph.D. from the University of Utah in Pharmaceutics and Pharmaceutical Chemistry. I have 12 years of experience conducting research in the areas of dermal and ophthalmic formulation development and leading project teams responsible for all CMC aspects of product development from phase 1 to phase 3 at Allergan, Inc.

3. I have read the above-captioned patent application and its pending claims as of the date of this Declaration. I have read the obviousness rejections made in the

Office Action dated December 1, 2014 and the publications cited by the patent examiner therein (International Patent Publication No. WO 2009/108147 A1, International Patent Publication No. WO 2010/105052 A1,US Patent Publication No. 2006/0204526, and the Lubrizol product description of Carbopol 980).

4. I am part of a team at Allergan responsible for developing a new formulation of Allergan's Aczone (dapsone) Gel, 5% product, wherein dapsone concentration is increased to 7.5% w/w from the 5% w/w level in Aczone 5% Gel. An object of this development project was to facilitate once daily dosing by increasing the concentration of dapsone, as compared to the current twice daily dosing regimen for Aczone 5% Gel.

5. During the course of development of the 7.5% w/w dapsone formulation, we looked to increase DGME concentration above the 25% level in Aczone 5% Gel in order to increase the saturation solubility of dapsone. Dapsone solubility increases with DGME concentration. This increase allows for a dissolved fraction of dapsone (dissolved fraction is calculated as the ratio of dapsone saturated solubility at 25 °C / dapsone concentration) comparable to that of Aczone 5% gel.

6. Under my supervision, a preliminary evaluation of thickeners suitable for use in the dapsone 7.5% gel formulation was performed. Five candidates were screened for their ability to thicken the proposed formulation: Carbopol® 980, Sepineo™ P 600, PPG-12/SMDI Copolymer (4,4'-Diisocyanatodicyclohexylmethane, polypropylene glycol polymer), Povidone/Eicosene (30:70), and Polyvinyl Alcohol. From this screening evaluation, we identified Carbopol 980 and Sepineo P 600 as promising gelling agents.

7. In additional experiments under my supervision, formulations containing Carbopol 980 showed undesired polymer aggregates at 40% diethylene glycol monoethyl ether ("DGME") concentration. This aggregation was not observed

with formulations containing Sepineo P 600 at 40% DGME. These results indicated that Sepineo P 600 is a more robust thickener and therefore more desirable for use in the gel formulation. I did not expect to observe Carbopol 980 incompatibility at a concentration of 40% DGME, especially because Carbopol 980 is compatible at concentrations of 25% DGME.

8. Based on the unexpected observation of Carbopol 980 incompatibility with 40% DGME, the thickener was changed from Carbopol 980 to Sepineo P 600 to mitigate the risk of polymer aggregation in DGME containing formulations.

9. In additional experiments under my supervision, a dapsone particle size assessment revealed that formulations thickened with Sepineo P 600 provided a smaller dapsone particle size as compared to Carbopol 980. The compositions of the formulations evaluated for particle size are outlined in Table 1 of Appendix A of this Declaration. Particle size data are provided in Table 2 (HORIBA data) of Appendix A of this Declaration. The data show that recrystallized dapsone particle size is smaller in the Sepineo P 600 formulation as compared to a Carbopol 980 formulation. I observed this difference even after 6 months storage under accelerated conditions (40 °C/75% RH) thereby showing no significant change in the particle size over time. This stability data suggests that particle size does not change over time irrespective of the stabilizer used (Carbopol or Sepineo). Thus a smaller initial particle size appears to be more relevant parameter that defines improved formulation characterization.

10. Based on the above results, my co-inventors and I selected Sepineo P 600 as the gelling agent for our dapsone 7.5% gel formulation. We made this selection due to Sepineo P 600's compatibility with concentrations of DGME greater than 25% and its improvement in dapsone particle size relative to Carbopol 980.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: February 2, 2015

Kevin S. Warner, Ph.D.

APPENDIX A

Table 1 **Composition of Formulations Analyzed for Dapsone Particle Size Comparison in Sepineo P 600 vs. Carbopol 980**

Component	% w/w		
	ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600	7.5% Dapsone, 25% DGME, 1% Carbopol	7.5% Dapsone, 30% DGME, 1% Carbopol
Dapsone	7.5	7.5	7.5
DGME	30	25	30
Carbopol 980	N/A	1	1
Sepineo P 600	4	N/A	N/A
Methylparaben	0.2	0.2	0.2
Triethanolamine	N/A	QS pH 5.5 – 6.5	QS pH 5.5 – 6.5
Purified Water	QS 100	QS 100	QS 100

N/A = Not Applicable

Table 2 **Particle Size (HORIBA) Data Comparing Dapsone Particle Size in Sepineo P 600 vs. Carbopol 980 at Time = 0 and 6 Months at 40 °C/75% RH**

Formulation Description	D90 (µm)	
	T=0	T=6 Months 40 °C/75% RH
ACZONE (dapsone) Gel, 7.5%: 7.5% Dapsone, 30% DGME, 4% Sepineo P 600 (Lot ELE)	61	72
7.5% Dapsone 25% DGME 1% Carbopol (Lot ELF)	123	114
7.5% Dapsone 30% DGME 1% Carbopol (Lot ELG)	172	169

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