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September 1, 2000

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**Re. Sunscreen Drug Products for Over the Counter Human Use; Monograph;
Extension of Effective Date; Reopening of Administration Record, FDA Docket No.
78N-0038**

Dear Sir or Madam:

These comments are filed on behalf of the Tayca Corporation and TRI-K Industries, Inc. in response to the *Federal Register* notice of June 8, 2000.

The Tayca Corporation is a producer of Titanium Dioxide based in Osaka, Japan. The Tayca Corporation produces fine particle size grades of Titanium Dioxide which have been used for over ten years in the manufacture of sunscreens in the US and world markets.

TRI-K Industries is a distributor of chemical ingredients to the United States cosmetic and personal care industry. TRI-K Industries is the sales and marketing channel for Tayca's fine particle size grade of Titanium Dioxide. TRI-K has represented Tayca in the US market for ten years. In addition, TRI-K possesses a technical service and applications development laboratory and supports their customers in the use and formulation of fine particle size grades of Titanium Dioxide for sunscreen applications.

I. Background and Summary of Comments:

These comments are submitted in order to make the Agency aware of the UVA attenuation properties of fine particle size grades of Titanium Dioxide. We will present both *in vivo* and *in vitro* data to demonstrate the significant consumer protection offered by fine particle size grades of Titanium Dioxide in both the UVA and UVB regions of the solar spectrum.

Based on the data provided, we request the agency to allow the full set of UVA broad spectrum claims (as cited in 61 FR 48645 and 63 FR 56584 for Avobenzone and Zinc Oxide, respectively) for sunscreen products containing Titanium Dioxide including the indication "Provides protection from the UVA rays that may contribute to skin damage and premature aging of skin."

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This consideration will allow marketers of sunscreen and skin care products greater flexibility in delivering significant consumer protection throughout the UVA and UVB regions.

II. Presentation of *In Vitro* and *In Vivo* Data:

The data presented herewith will demonstrate the following properties of sunscreens containing commercially and economically realistic concentrations of USP grade Titanium Dioxide:

1. Titanium Dioxide containing sunscreens can offer significant UVB protection as indicated by SPF value.
2. Titanium Dioxide containing sunscreens can meet *in vitro* critical wavelength criteria for broad spectrum claims of 370 nm.
3. Titanium Dioxide containing sunscreens can offer UVA protection as measured by the *in vivo* Persistent Pigment Darkening (PPD) method.
4. Titanium Dioxide containing sunscreens can offer UVA protection as measured by the *in vitro* UVA Protection factor method.
5. Increases in Titanium Dioxide containing sunscreens SPF are accompanied by a proportional increase in UVA protection.

Nineteen prototype formulations containing Titanium Dioxide were developed. All Titanium Dioxide containing formulations employed USP grade material.

Various particle sizes of Titanium Dioxide were evaluated including pigmentary grade (larger particle size) product.

A variety of different formulations were evaluated including oil-in-water and water-in-oil emulsion systems.

Reference formulations included a negative control (no UV absorbers) and positive controls that contained recognized UVA sunscreen agents Avobenzone and Zinc Oxide.

A. *In Vitro* SPF, Critical Wavelength, and UVA Protection Factor Study

Table I shows summary UVB and UVA protection data for 27 prototype sunscreen formulations based on measurements from the Optometrics SPF 290 Analyzer. Each UVB and UVA value presented below is the average of two experiments. Pertinent information describing the method and instrument in detail is found in Appendix 1.

Table I – In Vitro UVB and UVA data

<u>Formula #</u>	<u>UV Screen</u>	<u>Sunscreen Concentration (Wt. %)</u>	<u>Formula type</u>	<u>TiO₂ particle size (nm)</u>	<u>SPF</u>	<u>UVA PF</u>	<u>Critical wavelength (nm)</u>
EK4-95E	TiO ₂	4.15	o/w	15	11.12	5.00	374.2
EK4-95B	TiO ₂	8.30	o/w	15	20.60	9.13	376.9
EK4-96A	TiO ₂	5.00	o/w	35	7.07	4.67	381.6
EK4-96C	TiO ₂	10.00	o/w	35	20.63	12.58	381.9
EK4-96	TiO ₂	4.15	o/w	30	4.84	3.18	380.6
EK4-96B	TiO ₂	8.30	o/w	30	15.17	8.07	379.0
EK5-3B	TiO ₂	3.70	o/w	15	7.97	3.79	375.0
EK5-3A	TiO ₂	7.40	o/w	15	16.48	7.53	376.2
EK4-96D	TiO ₂	5.00	o/w	180	3.81	3.09	384.1
EK4-96E	TiO ₂	10.00	o/w	180	8.31	6.29	382.5
EK3-74C	TiO ₂	6.64	o/w	15	16.10	6.50	373.0
EK3-7A	TiO ₂	4.32	o/w	15	8.10	4.15	378.2
EK5-3C	TiO ₂	3.70	o/w	15	8.52	4.17	375.1
EK3-78A	TiO ₂	4.15	w/o	15	7.75	3.50	373.5
EK3-78C	TiO ₂	6.64	w/o	15	14.60	6.35	374.5
EK2-89B	TiO ₂	6.92	w/o	15	12.57	5.77	378.8
EK2-89C	TiO ₂	8.65	w/o	15	21.85	8.99	378.7
EK4-3	TiO ₂	4.15	w/o	30	5.49	3.53	383.2
EK4-100A	TiO ₂	7.40	w/o	15	35.37	14.60	371.5
EK4-99	No active	0.00	o/w	n/a	1.13	1.06	377.5
EK4-99A	Avobenzone	2.00	o/w	n/a	5.23	13.37	379.3
EK4-99B	Avobenzone	3.00	o/w	n/a	9.86	27.60	379.7
EK4-3B	Avobenzone	3.00	w/o	n/a	5.44	8.68	382.4
EK4-97	ZnO	4.90	o/w	n/a	3.12	2.71	379.7
EK4-97A	ZnO	9.80	o/w	n/a	8.78	7.14	379.3
EK5-4	ZnO	4.90	w/o	n/a	2.27	1.93	378.6
EK3-28B	ZnO	9.80	w/o	n/a	5.70	4.70	379.0

The formulations for each of the tested prototypes combined with their Optometrics 290 SPF Analyzer data are compiled in Appendix 2.

The *in vitro* data reported in Table I shows that both UVB and UVA results are dependent on a number of formulation factors including ingredients used, emulsion type, and Titanium Dioxide concentration and particle size. However, all of the formulations demonstrate that significant UVB and UVA protection is possible with Titanium Dioxide containing sunscreens.

1. UVB Protection – Titanium Dioxide concentrations ranging from 3.70% to 10.00% resulted in a range of SPF values from 3.81 to 35.37.

2. Critical Wavelength – All nineteen formulations containing Titanium Dioxide possessed critical wavelength values greater than 370 nm (range 371.8 nm to 384.1 nm).

3. UVA Protection Factor – Fourteen out of the nineteen formulations containing Titanium Dioxide exhibited UVA Protection Factors greater than 4 (range 3.09 to 14.50).

B. In Vivo SPF, Critical Wavelength, and PPD Study

Clinical studies measuring the SPF and PPD of four of the formulations from the *in vivo* experiment were performed by AMA Laboratories, New City, New York. Twenty subjects were used for the SPF tests and ten subjects were used for the PPD study. Table II shows both the *in vivo* UVB and UVA data for these formulations and comparisons to the *in vitro* data.

Table II - Comparison of *in vivo* and *in vitro* UVA and UVB data.

<u>Formula</u>	<u>TiO₂</u>	<u>In Vivo SPF</u>	<u>In Vitro SPF</u>	<u>PPD</u>	<u>UVA PF</u>	<u>Critical</u>
	<u>Concentration</u>				<u>(in vitro)</u>	<u>Wavelength</u>
						<u>(nm)</u>
EK4-95E	4.15	10.76	11.12	4.79	5.00	374.2
EK4-95B	8.30	18.31	20.60	9.17	9.13	376.9
EK4-96A	5.00	10.00	7.07	4.58	4.67	381.6
EK4-96C	10.00	18.41	20.63	8.80	12.56	381.9

The full study report by AMA Laboratories is included as Appendix 3.

Based on the clinical studies, the data demonstrate significant UVB and UVA protection of Titanium Dioxide. SPF values ranged from 10.00 to 18.41 and PPD values ranged from 4.58 to 9.17. In addition, an excellent correlation is found between both the *in vivo* and *in vitro* SPF data as well as the PPD and UVA PF results.

C. Illustration of Proportionality Between UVB and UVA Protection for Titanium Dioxide Containing Sunscreens

Sunscreen formulations based on Titanium Dioxide demonstrate proportionality of UVB and UVA protection. To illustrate this, SPF and UVA measurements, both *in vivo* and *in vitro*, were made on pairs of formulations where only the Titanium Dioxide concentration differed. Results for two of these pairs of formulations were reported in Table II. For example, formulations EK4-95E and EK4-95B were identical in composition except for the differing Titanium Dioxide concentrations of 4.15% and 8.30% respectively. Formulations EK4-96A and EK4-96C are a similar pair, differing in Titanium Dioxide concentrations by a factor of two.

The ratio of UVB increase to UVA increase is calculated as follows:

$$\frac{(SPF_{high}/SPF_{low})}{(PPD_{high}/PPD_{low})}$$

or

$$\frac{(SPF_{high}/SPF_{low})}{(UVA\ PF_{high}/UVA\ PF_{low})}$$

Proportionality in protection is indicated when this ratio is close to 1. A ratio value less than 1 indicates greater increases in UVA protection compared to the SPF increase.

Table III shows this ratio for the two pairs of formulations reported in Table II.

Table III - Ratio of increase in UVB to UVA protection

<u>Formulation Pair</u>	<u>Ratio of UVB to UVA protection increase</u>
EK4-95E v. EK4-95B (in vivo)	0.89
EK4-96A v. EK4-96C (in vivo)	0.96
EK4-95E v. EK4-95B (in vitro)	1.01
EK4-96A v. EK4-96C (in vitro)	1.08

Each of the formulation pairs exhibits UVB increase to UVA increase ratios of 1 +/- 11%, maximum. This demonstrates that for Titanium Dioxide containing sunscreens, when UVB protection increases, UVA protection (measured *in vivo* or *in vitro*) increases by a similar proportion.

III. Conclusion and Recommendations:

The data presented show clearly that Titanium Dioxide containing sunscreens, in addition to providing excellent UVB protection, can meet all the criteria for UVA protection recommended by the American Academy of Dermatology¹.

Based on these facts, we urge the Agency to view Titanium Dioxide as a sunscreen active which can offer significant consumer protection in both the UVB and UVA regions of the solar spectrum and permit users of Titanium Dioxide access to the full set of UVA/Broad Spectrum label claims including those which relate to protection against skin damage and premature aging.

Respectfully submitted,



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References:

1. Summary of the American Academy of Dermatology Consensus Conference on UVA Protection of Sunscreens, Washington, D.C., February 4, 2000.