



THE COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION

January 14, 2000

Charles J. Ganley, M.D.
Director
Division of OTC Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

E. EDWARD KAVANAUGH
PRESIDENT

Re: Final Regulation for Sunscreen Drug Products (Docket No. 78N-0038)

Dear Dr. Ganley:

This letter is written in response to requests by the Food and Drug Administration ("FDA") at the Sunscreen Working Group Meeting on October 26, 1999 for additional data regarding the testing and labeling of high sun protection factor ("SPF") sunscreen drug products. It is submitted on behalf of The Cosmetic, Toiletry, and Fragrance Association (CTFA) and the Consumer Healthcare Products Association (CHPA) which represent the interests of sunscreen manufacturers and marketers.

We appreciate the comments raised in the FDA presentations at the Meeting. Enclosed please find additional data, specifically a copy of the neutral density data comparison report (with four Tables of data), plus specific comments on the various technical issues raised in our discussions. We intend to submit the methods validation materials on the two control standards, as well as suggested labeling in separate submissions to the Agency as soon as possible after the first of the year.

Our goal is to ensure that the Agency has the information necessary to revise the Final Monograph for Sunscreen Drug Products to allow all properly-substantiated SPF claims without placing any arbitrary limit on the ability of manufacturers to make those claims. We believe that labeling information that accurately describes the level of sun protection provided by each product is critical to consumer decision-making to obtain adequate protection from all the harmful effects of the sun. We believe that the materials already in the rulemaking record together with the additional material that will be provided in response to FDA's questions should resolve any doubts regarding the validity of these claims.

1101 17TH ST., N.W., SUITE 300 WASHINGTON, D.C. 20036-4702

202.331.1770 FAX 202.331.1969

<http://www.ctfa.org>

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Sunscreen SPF Testing Methodology

The ability of current SPF test methods to produce accurate and reproducible values for sunscreen products with high SPFs was questioned by the Agency in the Sunscreen Final Rule (monograph) and in the Feedback Letter of September 2, 1999. New data, which were initially presented at the Feedback meeting of July 22, 1999, were provided in more detail to the Agency in advance of the FDA Sunscreen Working Group meeting of October 26 and served, in part, as the basis for further discussions on several of the methodology questions at the meeting on October, 26, 1999.

Solar Simulator Specifications and Limits

CTFA supports the adoption of the internationally accepted specifications (COLIPA) for solar simulators which were submitted by CTFA in 1994 (Docket 78N-0038, Comment C361). Based on the discussion with Dr. Sharon Miller at the meeting on October 26, we believe that the table of spectral power distribution for solar simulators as outlined on page 3 of the FDA's September 2 Feedback Letter (e.g., COLIPA solar simulator emission spectrum, with a modification to limit the energy <290 nm to <0.1%) would be appropriate for standardizing light sources used in sunscreen SPF testing. While we believe that it is possible to meet the limit of "less than 0.1% of the erythemally effective radiation below 290 nm", we are not aware that it is either practical or feasible to set a limit as low as 0.01% due to the limitations of the measuring devices available today. We are also not aware that filters to allow a 0.01% limit have been identified or are available.

A total irradiance limit of 1500 watts/meter² seems appropriate in our experience for testing sunscreen products without delivering excessive heat to the skin. A lower limit would only serve to make SPF tests longer and more costly and would pose a hardship on test subjects, but would not add value to test accuracy.

To demonstrate that there is no measurable impact of heat load on the outcome of SPF testing when operated within the parameters above, we are providing data in Attachment 1 which offer a comparison of results using solar simulators with and without an additional 50% neutral density filter. As can be observed from the data provided, the use of the neutral density filter, in addition to the standard WG320/UG-11 filter set, did not affect the overall results for either an SPF 15 formulation or an SPF 30 formulation.

High SPF Sunscreen Control and Assay Methods

Based on extensive experience with the SPF 15 control, we believe that the formulation recommended as the SPF 15 control preparation can be prepared and assayed successfully. Methods validation packages for the SPF 15 and for the SPF 4 control formulations will be provided to the Agency by early February, 2000.

Use of Control Preparations in the SPF Test

The purpose of the "control" preparation is to help ensure adequate laboratory methodology and procedures, and not to serve the purpose of an analytical standard. In that sense, the control preparation is independent of its specific SPF value. Therefore, either of the control preparations (SPF 4 or SPF 15) should be acceptable for discriminating whether or not the product application technique used and/or the UV exposures given, were carried out in an acceptable manner.

From a practical perspective, when using a COLIPA-compliant solar simulator and a total irradiance of less than 1500 watts/meter², the time needed in the laboratory to conduct a "Very Water Resistant" test (TFM or Final Monograph method, 7 exposures) on a product with an SPF > 30 can exceed 5-6 hours. A significant amount of that time is spent in delivering the UV exposures. With the addition of the SPF 15 control preparation, test times would be extended by at least one additional hour. In many laboratories, it is not possible to test two products with an SPF of 30 or higher on the same subject on the same day due to the lengthy testing process. We do not believe, therefore, that a test standard higher than SPF 15 is needed for laboratory methodology control. Further, use of such a standard would not be practical considering testing time duration constraints. In addition, it is beyond the practical endurance capabilities of many test subjects to spend more than 5-6 hours sitting still in front of a UV light source. Subject fatigue can lead to errors in the test results due to the potential for subjects to be unable to comply with testing requirements during very long exposure times.

Number of Test Subjects

The data contained in the previously submitted report "Testing High SPF Formulations: A Comparison of the Accuracy and Reproducibility of the Results of Testing Three High SPF Formulations by Two Methods" provided information which was reviewed by Dr Srinivasan on the issue of the acceptable number of test subjects needed for high SPF formulation testing. Based on the review of those data, it was concluded that 20-25 subjects are adequate to obtain acceptable data on high SPF formulations. If statistically acceptable data are not obtained within a panel of 20-25 subjects, the Agency suggested possibly allowing additional subjects to be tested to obtain more data. However, a high test failure rate or a very wide spread of data may signal either formulation or laboratory test methods problems; the panel size along with statistical limits should still serve to weed out poor formulas. We suggest that a panel of 20-25 subjects is adequate for testing high SPF formulations if the data fall within acceptable statistical parameters. If data from the panel of 20-25 subjects are not definitive, a panel of "at least 20-25 subjects, with additional subjects added to confirm the SPF value, with the requirement that $\geq 80\%$ of the total panel provides valid data" might be appropriate. However, it should not be necessary to require costly larger panels if the data from the first 20-25 subjects are acceptable.

It is interesting to note that the regulations for determining SPF values for products labeling in both Japan and Australia require valid data only from "at least 10 subjects"; the COLIPA/EU method requires valid data from a "minimum of 10 to a maximum number of 20" subjects, based on statistical considerations. These requirements apply to all SPF levels.

Exposure Doses

The data provided in the previously submitted report "Testing High SPF Formulations: A Comparison of the Accuracy and Reproducibility of the Results of Testing Three High SPF Formulations by Two Methods" illustrated that the use of either the 25% exposure increment series or the 15% increment series can result in similar SPF values for the test panel. These data showed that the variability of the data fits within the acceptable statistical parameters outlined in both the Proposed or the Tentative Final Monograph's statistical requirements for determining the label SPF value, regardless of the exposure increment series used. For that reason, we feel that the current methodologies are adequate relative to the exposure series proposed.

However, we do not believe, based on available data, that the series of seven exposures (including the half-increments around the mid point) provides more precise data, due to the inherent biological variability of subjects' skin responses. When the MED of the test series does not turn out to be the predicted midpoint, the "half-increment" exposures do not add value or accuracy to the test and only serve to prolong the overall test procedure. The five-exposure, 25% increment series appears to be as accurate for a full panel of subjects as is the smaller (15%) increment series, even at high SPFs. Both methods can provide comparable and acceptable data.

To avoid exposing test subjects to unnecessary UV radiation and prolonging an already lengthy test procedure (which is often uncomfortable and tiring for test subjects), we urge the Agency to revise the testing requirement to eliminate the "half-increment exposures". With the elimination of that requirement, we agree that the series of five exposures (at 25%, 20% or 15%, depending on SPF) would be acceptable.

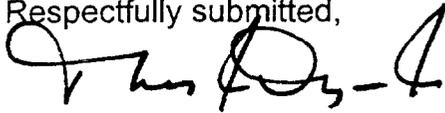
Labeling

Our industry has strived to communicate the benefits of using sunscreens as part of an overall sun protection program. The use of high-SPF sunscreen drug products is an important component of the public health message that consumers need to protect themselves against sub-erythral damage and that high-SPF products also provide correspondingly increasing UVA protection. As such, we believe that high-SPF claims should be justified by good science rather than a numerical limit. We also believe that the benefits of using these products can be conveyed in a clear and comprehensive manner.

As requested by FDA, we are currently considering additional labeling appropriate for communicating the level of sun protection associated with high-SPF sunscreen products. We will provide our recommendations to the Agency as soon as possible.

We look forward to working with the Agency to resolve these technical questions, as well as the critical issues associated with UVA testing and labeling.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Thomas Donegan, Jr.", with a stylized flourish at the end.

Thomas J. Donegan, Jr.
Vice President-Legal & General Counsel

attachment

cc: Robert DeLap, M.D. (HFD-105)
Linda M. Katz, M.D. (HFD-560)
John Lipnicki (HFD-560)
Dockets Management Branch (HFA-305)

ATTACHMENT 1

**A COMPARISON OF THE RESULTS OF TESTING TWO
SUNSCREEN FORMULATIONS WITH AND WITHOUT A
50% NEUTRAL DENSITY FILTER**

**SCHERING-PLOUGH HEALTHCARE PRODUCTS
NOVEMBER 1999**

Introduction

In our laboratory, xenon arc solar simulators are used routinely for conducting SPF testing. The primary type of solar simulator used is the 150-watt xenon arc, filtered with 1-mm WG320 and UG11 filters to remove UV energy below 290 nm and to remove excess heat. Several 150-watt solar simulators are available for use in the laboratory at any one time; they rotate in and out of service as they undergo routine maintenance, which may include filter and/or lamp replacements. While each instrument, therefore, has a unique "total irradiance", they are operated within the 1500 W/m² total irradiance limit recommended by CTFA in 1994 (docket 78N-0038, comment C361).

Because concerns have been raised that the heat load on the skin during the testing of formulations with high SPFs could affect dose-reciprocity and thus also affect the test outcome (i.e., the SPF value), we retrospectively compared the results of studies in which two different formulations had been tested with and without a 50% neutral density filter. This data comparison was made to determine if reducing the dose rate had resulted in any measurable change in the testing outcome.

Materials and Methods

SPF test results from two formulations were included in this data comparison. Each panel of data represents an independent, autonomous panel, tested in our laboratory as part of ongoing formula development over the past several years.

Formula 1: SPF 15

("CTFA control standard SPF 15 lotion"):

active ingredients: oxybenzone
Padimate O

Formula 2: SPF 30 prototype (an experimental formulation)

active ingredients: oxybenzone
homosalate
octyl methoxycinnamate
octyl salicylate
avobenzone

Results

The test data and data summaries are shown in Tables 1, 2, 3 and 4.

Tables 1 and 2 show the data obtained by testing the SPF 15 control lotion using the 1978 FDA Proposed Monograph SPF testing method (25% UV exposure increment series). In Table 1, data from 47 subjects are shown. These subjects were tested in our laboratories during a one month timeframe in studies which included the SPF 15 control lotion. These

tests did not include a neutral density filter. The data show that the formulation had a mean SPF of 16.18 for the subjects tested.

Table 2 includes data from testing the SPF 15 control preparation using 150-watt xenon arc solar simulators, with the addition of a 50% neutral density filter. The mean SPF for this panel was 16.76.

Tables 3 and 4 show the data obtained by testing the SPF 30 prototype formulation with and without the neutral density filter.

The first test of the SPF 30 formulation, using the 1978 Proposed Monograph "Waterproof" test method (25% exposure increments), included the 50% neutral density filter. Those data are shown in Table 3. The mean SPF value for the panel of 21 subjects was 34.44.

In Table 4, data from 23 subjects are shown. This panel (tests performed according to the 1993 Tentative Final Monograph "Very Water Resistant" method; 15% exposure increments) did not include the neutral density filter. The data show that the SPF 30 prototype formulation had a mean value of 33.67 for the subjects tested in that panel.

Discussion

The data shown in Tables 1 and 2 include SPF test panel results for the SPF 15 control preparation, tested by the 1978 Proposed Monograph test method, with and without the use of a 50% neutral density filter. These data illustrate that both panels of subjects exhibited comparable results; that is, the use of the neutral density filter did not impact the testing outcome.

The data shown in Tables 3 and 4 include panels of SPF test results for a prototype formulation with an expected SPF of 30, tested once by the 1978 Proposed Monograph test method with the addition of the neutral density filter, and in a second panel of subjects by the method described in the 1993 Tentative Final Monograph, but without the neutral density filter. These data illustrate that the use of the neutral density filter did not impact the overall test outcome for this formulation.

Conclusions

While the data provided in Tables 1 through 4 do not provide a direct "within subjects" comparison of results from panels tested with and without the neutral density filters, these data clearly support the conclusion that there is no negative effect on UV dose-reciprocity in SPF testing due to thermal overload of the skin, when testing is conducted using solar simulators filtered with WG320/UG11 filter sets to meet COLIPA specifications. UV dose reciprocity is maintained when testing is conducted with the total

irradiance level maintained below the proposed 1500 W/m² irradiance limit. With or without the use of the neutral density filters, the test outcomes were consistent for the two formulations tested. Therefore, the combination of the COLIPA energy emission specifications with the 1500 W/m² total irradiance limit offers a reasonable way to describe and control solar simulators used for SPF testing. It has been demonstrated that there is no negative impact on dose-reciprocity and no adverse effects of thermal overload of the skin seen when solar simulators are operated within these limits; therefore, we recommend that these parameters be adopted by FDA.

References

- COLIPA: Sun Protection Factor Test Method, ref. 94/289, October 1994.
Federal Register: May 12, 1993 (Volume 58, Number 90), Tentative Final Monograph pp. 28194-28302.
Federal Register: August 25, 1978 (Volume 43, Number 166), Proposed Rulemaking pp. 38206-38269.

TABLE 1
SCHERING-PLOUGH HEALTH CARE PRODUCTS
SPF TEST SUMMARY REPORT

Product: CONTROL: "CTFA STANDARD 15"
Protocol: STATIC SPF (1978 Method, 25% exposure increments) (No Neutral Density Filter)
Active Ingredients: PADIMATE O (7.00%) OXYBENZONE (3.00%)

Subject	MED	Ctl MED	Actual SPF	Comments
1	188	10	18.80	
2	150	10	15.00	
3	240	20	12.00	
4	305	13	23.46	
5	150	8	18.75	
6	150	10	15.00	
7	244	13	18.77	
8	244	13	18.77	
9	150	10	15.00	
10	234	13	18.02	
11	240	16	15.00	
12	195	16	12.19	
13	188	10	18.80	
14	240	20	12.00	
15	156	13	12.00	
16	188	10	18.80	
17	240	16	15.00	
18	188	10	18.80	
19	188	10	18.80	
20	188	8	23.50	
21	150	10	15.00	
22	> 188	8	> 23.50	
23	150	16	9.38	
24	195	13	15.00	
25	195	13	15.00	
26	150	10	15.00	
27	156	10	15.60	
28	244	13	18.77	
29	244	13	18.77	
30	192	16	12.00	
31	120	10	12.00	
32	2438	163	14.96	SS#1 *
33	1950	130	15.00	SS#1 *
34	3047	130	23.44	SS#1 *
35	1920	199	9.64	SS#1 *
36	1875	125	15.00	SS#1 *
37	180	12	15.00	
38	150	10	15.00	
39	150	10	15.00	
40	195	10	19.50	
41	188	13	14.47	
42	1560	83	18.80	SS#1 *
43	1248	83	15.04	SS#1 *
44	2438	130	18.75	SS#1 *
45	1556	83	18.75	SS#1 *
46	1560	130	12.00	SS#1 *
47	2438	130	18.75	SS#1 *

*Data were obtained using a 150-watt filtered xenon arc solar simulator, except for the 11 values noted as "SS#1", which were obtained using a filtered 2500-watt xenon arc system.

TEST SUMMARY

Mean SPF: 16.18	FM SPF: 15
Number Tested: 47	Number Calculated: 46
Standard Deviation: 3.34	
Standard Error: 0.50	Percent Standard Error of Mean: 3.08

TABLE 2

SCHERING-PLOUGH HEALTH CARE PRODUCTS
SPF TEST SUMMARY REPORT

Product: CONTROL: "CTFA STANDARD SPF 15"

Protocol: STATIC SPF (1978 Method, With 50% NEUTRAL DENSITY FILTER)

Active Ingredients: PADIMATE O (7.00%) OXYBENZONE (3.00%)

Subject	MED	Ctl MED	Actual SPF	Comments
1	300	20	15.00	SS#3 50% ND FILTER
2	300	16	18.75	SS#3 50% ND FILTER
3	586	31	18.90	SS#7 50% ND FILTER
4	375	25	15.00	SS#7 50% ND FILTER
5	586	31	18.90	SS#7 50% ND FILTER
6	240	20	12.00	SS#4 50% ND FILTER
7	240	16	15.00	SS#7 50% ND FILTER
8	300	25	12.00	SS#4 50% ND FILTER
9	> 469	31	> 15.13	SS#4 50% ND FILTER
10	240	20	12.00	SS#6 50% ND FILTER
11	375	20	18.75	SS#6 50% ND FILTER
12	375	20	18.75	SS#6 50% ND FILTER
13	469	20	23.45	SS#7 50% ND FILTER
14	375	20	18.75	SS#5 50% ND FILTER
15	300	20	15.00	SS#4 50% ND FILTER
16	240	20	12.00	SS#7 50% ND FILTER
17	727	39	18.64	SS#4 50% ND FILTER
18	300	20	15.00	SS#6 50% ND FILTER
19	469	20	23.45	SS#7 50% ND FILTER
20	300	20	15.00	SS#7 50% ND FILTER
21	469	25	18.76	SS#4 50% ND FILTER

TEST SUMMARY

Mean SPF: 16.76

FM SPF: 15

Number Tested: 21

Number Calculated: 20

Standard Deviation: 3.49

Standard Error: 0.80

Percent Standard Error of Mean: 4.78

TABLE 3

SCHERING-PLOUGH HEALTH CARE PRODUCTS
SPF TEST SUMMARY REPORT

Product: SPF 30 Prototype

Protocol: WATERPROOF SPF (1978 Method, With 50% Neutral Density Filter)

Active Ingredients: OXYBENZONE, HOMOSALATE, OCTYL METHOXYCINNAMATE,
OCTYL SALICYLATE, AVOBENZONE

Subject	MED	Ctl MED	Actual SPF	Comments
1	938	20	46.90	SS#6 50% ND FILTER
2	480	25	19.20	SS#3 50% ND FILTER
3	976	32	30.50	SS#4 50% ND FILTER
4	750	25	30.00	SS#7 50% ND FILTER
5	750	20	37.50	SS#3 50% ND FILTER
6	I	I	I	TEST INCOMPLETE
7	750	20	37.50	SS#4 50% ND FILTER
8	900	24	37.50	SS#4 50% ND FILTER
9	750	25	30.00	SS#4 50% ND FILTER
10	750	25	30.00	SS#7 50% ND FILTER
11	750	25	30.00	SS#3 50% ND FILTER
12	938	25	37.52	SS#7 50% ND FILTER
13	938	25	37.52	SS#3 50% ND FILTER
14	600	20	30.00	SS#3 50% ND FILTER
15	750	20	37.50	SS#3 50% ND FILTER
16	480	16	30.00	SS#7 50% ND FILTER
17	1453	39	37.26	SS#4 50% ND FILTER
18	600	16	37.50	SS#4 50% ND FILTER
19	600	16	37.50	SS#7 50% ND FILTER
20	750	20	37.50	SS#3 50% ND FILTER
21	750	20	37.50	SS#3 50% ND FILTER

TEST SUMMARY

Mean SPF: 34.44

FM SPF: 32

Number Tested: 21

Number Calculated: 20

Standard Deviation: 5.73

Standard Error: 1.31

Percent Standard Error of Mean: 3.81

TABLE 4

**SCHERING-PLOUGH HEALTH CARE PRODUCTS
SPF TEST SUMMARY REPORT**

Product: SPF 30 Prototype

Protocol: VERY WATER RESISTANT SPF (1993/TFM Method) (No Neutral Density Filter)

Active Ingredients: OXYBENZONE, HOMOSALATE, OCTYL METHOXYCINNAMATE,
OCTYL SALICYLATE, AVOBENZONE

Subject	MED	Ctl MED	Actual SPF	Comments
1	690	25	27.60	
2	635	16	39.69	
3	809	20	40.45	
4	1230	25	49.20	
5	< 703	39	< 18.03	
6	600	20	30.00	
7	992	31	32.00	
8	750	25	30.00	
9	600	25	24.00	
10	750	20	37.50	
11	863	25	34.52	
12	750	31	24.19	
13	690	20	34.50	
14	930	25	37.20	
15	992	31	32.00	
16	< 567	20	< 28.35	
17	750	25	30.00	
18	552	16	34.50	
19	< 454	20	< 22.70	
20	522	20	26.10	
21	522	16	32.63	
22	480	16	30.00	
23	417	16	26.06	

TEST SUMMARY

Mean SPF: 32.6

FM SPF: 30

Number Tested: 23

Number Calculated: 20

Standard Deviation: 6.18

Standard Error: 1.42

Percent Standard Error of Mean: 4.35