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September 1, 2000

Docket Management Branch  
Docket No. 78N-0038 (HFA-305)  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20857

Re: *Docket No. 78N-0038 – Sunscreen Products for Over-the-Counter Human Use*

Dear Sir/Madame:

We are responding on behalf of our client, L'Oréal Research/ L'Oréal USA (formerly known as Cosmair Cosmetics Corporation). Specifically, we have carefully reviewed the concerns expressed by The Procter & Gamble Company (Procter & Gamble) in their letter of May 2, 2000 to Docket 78N-0038, referenced below, as well as those raised by Dr. Brian Diffey in his letter of May 26, 2000 to Docket 78N-00388. THE WEINBERG GROUP INC. performed the statistical analyses utilized in the validation of the Minimal Persistent Pigment Darkening (PPD) method for UVA efficacy. In considering the above-mentioned comments of Procter & Gamble and Dr. Diffey, we address below statistical questions raised and relevant issues related to sunscreen product activity and efficacy.

## STATISTICAL ISSUES

In *Part 2* of the March 3, 2000 L'Oréal submission, we considered the statistical analyses raised by the Procter & Gamble and Dr. Diffey's comments. At that time, however, we believed that these analyses were not required to assess and interpret the data on Minimal Persistent Pigment Darkening (PPD) as an *in vivo* methodology to test UVA protection of sunscreen products. Since the comments have raised certain concerns about our statistical methodology, we have enclosed these updates to further elucidate the utility of the PPD test method.

It is clear from our analysis that, as expected and addressed qualitatively in the L'Oréal submission, differences in PPD determinations for the same product are found *between*

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laboratories. This result is clearly related to the decision not to standardize light sources or control products between laboratories as the study was designed to assess the suitability of the PPD method under actual conditions in a commercial testing environment (similar to current testing conditions accepted for SPF testing). In addition, while variation in interpretation of the PPD endpoint and application of product may be expected between laboratories, variation should be minimal in the way in which laboratories rate the same product. In statistical terms, there should be no interaction between study sites and products. Our results, presented below in the analysis of the interaction between study sites and products confirm that this is the case. Further, in an effort to reduce confusion regarding the expected differences between study sites, we also calibrated the results to eliminate differences between study sites. The results of this adjusted analysis are also presented in this letter.

In Section II Part B.3 of their May 2, 2000 response to Docket No. 78N-0038, Procter & Gamble raised questions about differences in UVA-PF determinations among study sites. Their claim is based on selected results of several nonparametric one-way analyses of variance. These analyses do not fully address the issue of whether or not there are differences among the study sites in the way they evaluate the relative effectiveness of the twelve products in providing UVA protection. The answer to this question can only be ascertained by performing factorial analysis of variance examining the interaction between study sites and products.<sup>1</sup> Table 1 summarizes the results of this analysis, which addresses biologically important differences among the study sites in the evaluation of the products.

**TABLE 1.**  
**RESULT OF A FACTORIAL KRUSKAL-WALLIS TEST COMPARING THE WAY**  
**IN WHICH STUDY SITES DETERMINE THE UVA-PF FOR TWELVE PRODUCTS.**

Factor	df <sup>1</sup>	H <sub>c</sub> <sup>2</sup>	P-value
Product	11	229.5	<0.00001
Site	2	18.5	0.00010
Interaction	22	20.5	0.55179

<sup>1</sup>Degrees of freedom

<sup>2</sup>Corrected Kruskal-Wallis test statistic

In Table 1, the interaction between product and site indicates the degree to which sites are consistent in the way in which they determine the relative effectiveness of the twelve products. The null hypothesis is that they are consistent. With a *P*-value of 0.55179, we demonstrate in a statistically appropriate analysis that the null hypothesis is not rejected.

Thus, it is appropriate to interpret each of the main effects individually. The main effects are

<sup>1</sup> Armitage P and Berry G. (1987) *Statistical Methods in Medical Research* 2<sup>nd</sup> edition. Blackwell Scientific Publications, Boston; p 227.



the differences between the products **not due to differences between the sites** (*i.e.*, the "product" main effect) and the differences between the study sites **not due to differences between the products** (*i.e.*, the "site" main effect).

Table 1 shows that the null hypothesis of no differences between the study sites, independent of differences between the products, can be rejected. This single null hypothesis subsumes all twelve of the null hypotheses tested by Procter & Gamble in their series of one-way analyses and, thus is less susceptible to errors in statistical inference than the multiple testing performed by Procter & Gamble. Finding differences between study sites is expected, as there was no attempt to standardize the study sites as part of the study's design. Even so, the differences between the study sites are impressively small. In illustration, Table 2 provides the overall mean UVA-PF values for each of the study sites.

**TABLE 2.**  
**OVERALL MEAN AND STANDARD DEVIATION OF UVA-PF VALUES IN EACH OF THE THREE STUDY SITES FOR THE TWELVE PRODUCTS.**

Site	Mean	SD
CPT	4.008	1.3429
HRL	4.716	1.5002
TKL	4.015	1.8291

The differences between the study sites can be controlled either by providing a calibration standard to each of the sites or by adjusting for these differences as part of data analysis. To do the latter, the differences between the means in each of the three sites were subtracted from all the values from that site. Table 3 illustrates the result of a factorial Kruskal-Wallis test on these adjusted values.

**TABLE 3.**  
**RESULT OF A FACTORIAL KRUSKAL-WALLIS TEST USING UVA-PF VALUES ADJUSTED FOR OVERALL DIFFERENCES BETWEEN STUDY SITES.**

Source	df	H <sub>c</sub>	P-value
Product	11	247.6	<0.00001
Site	2	0.8	0.67032
Interaction	22	19.0	0.64533

In Table 3, the only factor that is statistically significant is the product tested reflecting the fact that the products have different abilities to block UVA. Thus, the observed differences between UVA-PF determinations at study sites can be eliminated by calibrating the sites.



Another question raised by the statistical analyses performed by Procter & Gamble is their use of correlation analyses. Interpretation of the magnitude of a correlation coefficient as a reflection of the strength of a biologic association is especially dangerous, yet this is the basis of three conclusions drawn by Procter & Gamble. Those conclusions are that:

- (1) *In vitro* SPF is not an “appropriate” predictor of *in vivo* SPF,
- (2) *In vitro* UVAPF is a “redundant” measurement of *in vitro* SPF, and
- (3) Critical wavelength is independent of *in vivo* SPF.

Drawing these conclusions from the observed magnitude of correlation coefficients is inappropriate, since those correlation coefficients are not estimated from simple random samples. As Armitage and Berry point out, “The restriction of validity of the correlation coefficient to situations in which both variables are observed on a random selection of individuals is particularly important.”<sup>2</sup> That is not the case here, since the products tested are not a random sample of all possible products.

The reason for this concern about how both variables are sampled when interpreting a correlation coefficient is that the magnitude of the correlation coefficient can be substantially altered by different methods of sampling. For example, the correlation coefficient in Fig. 11 of Procter & Gamble’s letter is primarily reflecting the two most extreme observations. If those two outliers are removed, the square of the correlation coefficient changes from their reported value of 0.74 to a value of 0.13. Another example is in Fig. 12 of Procter & Gamble’s letter. Here, they have excluded data from products G, K, and L because they “had estimated SPF values.” The square of the correlation coefficient excluding those three products is equal to 0.85. If they had included those three products, however, they would have obtained a value close to 0.3 instead of greater than 0.8. Further, these data represent only those collected by the TKL Research site. If data of either of the other sites had been selected for this demonstration, the square of the correlation coefficient would have been even smaller (close to 0.2).

Since the magnitude of correlation coefficients is the only basis for the three biologic conclusions listed above and since interpreting the magnitude of correlation coefficients is inappropriate for these data, the biologic conclusions are without statistical support.

Thus, the correlation analyses presented by Procter & Gamble have been inappropriately applied and, as a result, misinterpreted. They do not provide support for any of their three opinions expressed above.

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<sup>2</sup> Armitage P and Berry G. (1987) *Statistical Methods in Medical Research* 2<sup>nd</sup> edition. Blackwell Scientific Publications, Boston; p 152.



## VALIDITY OF *IN VITRO* vs. *IN VIVO* METHODOLOGY

A further review of the comments in the Procter & Gamble letter identified a number of other issues that require clarification. These issues primarily revolve around the utility of an *in vitro* methodology to assess efficacy of a drug product. These concerns are discussed below with reference to specific comments contained in the Procter & Gamble letter.

- *On page 3, Procter & Gamble disagrees with our statement that the critical wavelength does not provide relevant data in a quantitative fashion. The following information is presented to clarify our position.*

Sunscreen products represent a drug delivery system. Critical wavelength provides *in vitro* evidence of the drugs' physical properties. This measurement provides no quantification of the dose required to achieve this level of UVA filtering or the frequency of drug administration required to maintain the filtering level. It is in this respect that we feel the critical wavelength method supported by Procter & Gamble fails to provide quantitative measures of the relevant *in vivo* correlate. In contrast, the PPD method does provide pivotal product efficacy data required to assess UVA protection. Clearly a measurement of the UVA spectrum of protection cannot equate to a quantification of *in vivo* efficacy. This is the singular and most significant failing of the critical wavelength measurement.

- *On pages 5 through 7, Procter & Gamble follow a series of arguments which lead to the conclusion that critical wavelength is in fact an appropriate way to measure efficacy in protecting against long wave exposure. Our disagreement with this assertion is outlined below.*

In the evaluation of any new drug, there needs to be data on the drug's specific activity (*i.e.*, binding to receptor site or similar surrogate for the expected *in vivo* activity). The critical wavelength is in effect a mere surrogate for the desired *in vivo* effect. It does not provide the necessary pharmacokinetic data to evaluate if in fact the product will be effective in delivering this activity to the target organ, in this case the skin.

The critical wavelength provides information that is similar to information that is available on ability to bind bile salts for a product like Questran®. Although the product is delivered orally, like sunscreens, it exerts its effect topically, albeit in the bowel. Before approving the product, FDA required demonstration that this *in vitro* characteristic would in fact lead to the expected *in vivo* effects of reducing cholesterol, or reducing itching from bile salts. By analogy, critical wavelength is a measure of the drug's specific activity (ability to filter UVA light) utilizing an artificial substrate. The PPD method provides a measure of product performance in protecting the skin from exposure to UVA rays. While an understanding of the physicochemical properties of the sunscreen and its absorbance spectra are necessary, they can never be sufficient to establish effectiveness.



- *On page 7, Procter & Gamble expresses concern that UVAPF and SPF measured in vitro are correlated. Outlined below are the reasons why we disagree with his assertion that one or the other is therefore redundant.*

As described above, we disagree with the manner in which correlations are interpreted by Procter & Gamble. In addition, both UVAPF and SPF could be important from the standpoint of the consumer. If a product label could ultimately have a SPF and UVAPF value, then the consumer would be informed as to the spectrum of its *in vivo* activity. This represents an advantage to the consumer, which also argues against the measures being redundant.

- *On page 9, Procter & Gamble expresses concern that the way protection factors are expressed could lead to false impressions of the magnitude of absorption differences. We disagree with this assertion for the reasons outlined below.*

The protection factors accurately express the product characteristics. Consumers purchase a product because the protection will be present for the time and at the level they require. In the derivation of PPD, a value of 10 is twice that of 5 because the subjects' pigmentation response took twice as long to develop in the PPD 10 product. The difference in absorption between the products is a physiochemical property of the product that is unrelated to the clinical effect which consumers are seeking from sunscreen. It is worth mentioning that the same correlative benefit exists for SPF values and consumer perception of the protection products currently offered against sunburn.

- *On page 9, Procter & Gamble raises concerns that protection factors are related to the dose or application density of the product.*

The clinical protection afforded to consumers will of necessity be related to the dose or application density of the product. By specifying the same dose or application density for both SPF and UVA evaluations, one is able to evaluate the protection ratio of a given product, an important parameter in the formulation of sunscreen products to ensure sufficient consumer protection across both the UVB and UVA spectrums. Clearly it is a major failing of the critical wavelength measurement that it provides no information on what dose or application density was used to provide the level of protection that the product label is claiming.

Because the critical wavelength is the same regardless of the dose or amount of product applied (application densities of both 1 mg/cm<sup>2</sup> and 2 mg/cm<sup>2</sup> have been previously assessed<sup>3</sup>) it provides no indication of the contribution of application density to the resulting affect. Only a suitable *in vivo* methodology is sufficient to address the

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<sup>3</sup> CTFA/NDMA Joint Sunscreen Task Force Report - Sunscreen Critical Wavelength Determination: A Method For Evaluating UVA Protection. Submitted to Docket 78N-0038 on April 9, 1996.



protection afforded following a controlled application. Furthermore, critical wavelength provides no information on the durability of the product with exposure to water, or other expected activities in everyday usage. In summary, a major failing of *in vitro* evaluations of sunscreen protection is the failure to provide information on the expected product performance when it is applied to the target organ under actually use conditions, a key requirement for approval of any new drug.

### COMPARISON TO SPF TESTING METHOD STANDARDS

Finally, the results of the March 3, 2000 L'Oreal submission should be considered in the context of the May 21, 1999 Final Monograph for Sunscreen Drug Products for Over-the-Counter Use. Comparison of the variability of the PPD method for determination of UVA protection to the accepted variability in methods for determining UVB protection, further demonstrates the viability of the PPD method. In this final monograph, conditions under which over-the-counter sunscreen drug products are generally recognized as safe and effective are addressed. Included are laboratory validation guidelines and acceptable standard deviation ranges for the standard sunscreen for use in SPF testing procedures (8% homosalate preparation with a mean SPF value of 4.47). Specifically, the Final Rule states: "In order for the SPF determination of a test product to be considered valid, the SPF of the standard sunscreen must fall within the standard deviation range of the expected SPF (i.e.,  $4.47 \pm 1.279$ ) . . ." Thus, the expected SPF of test sunscreens should fall within a coefficient of variation (CV) of 28.6%.

As a part of our original evaluation of the suitability of the PPD method for determination of the UVA protection factor (UVA-PF) the variability of UVA-PF for various sunscreen products was evaluated and compared to the variability observed with standard SPF testing of the control product used at each of the laboratories. For this evaluation, each of the three laboratories involved in testing the PPD method selected their own control sunscreen product. In all cases, the coefficient of variation (CV) for the UVA-PF measurements using the PPD method was below 28.6%, the CV calculated from the required range for SPF control products. Thus, the variability of the PPD method is consistent with acceptable ranges associated with biological testing parameters and comparable to the variability expected for SPF utilizing accepted and recognized methods as required by the FDA Final Rule on Sunscreen Drug Products for Over-the-Counter Human use.

In summary, we believe that our initial evaluation of the PPD multi-center evaluation presented in the L'Oréal submission and the clarifications above clearly address the relevant statistical and scientific concerns regarding *in vivo* sunscreen testing for UVA efficacy. The consistency of these data within laboratories is clearly demonstrated. The minor inconsistencies between laboratories can easily be removed with a simple calibration as



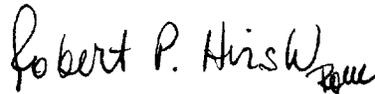
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demonstrated above. In addition, the significant shortcomings of an *in vitro* only method for product analysis are elucidated. The failure of the *in vitro* test to address the issues of activity at the target organ make this test inadequate to demonstrate efficacy of a drug substance.

Very truly yours,



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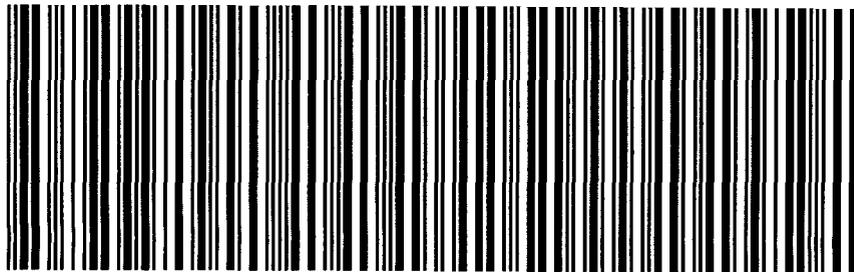


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