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

Re: Docket number 98N-0339

The following comments are provided by the Cosmetic Ingredient Review (CIR) as stakeholder input to the FDA on the matters described below.

***BACKGROUND ON CIR***

The Cosmetic Ingredient Review was established in 1976 by the Cosmetic, Toiletry, and Fragrance Association (CTFA). CIR is a unique endeavor to assess the safety of ingredients used in cosmetics in an unbiased, expert manner. Although funded by CTFA, CIR and the review process are distinctly separate and independent from CTFA and the cosmetic industry.

The heart of the CIR program is the independent Expert Panel consisting of world-renowned physicians and scientists. In addition, the Consumer Federation of America, and CTFA provide liaison members. The Food and Drug Administration (FDA) has a contact person who also participates. Expert Panel safety assessments are published in the *International Journal of Toxicology*, a widely-distributed, peer-reviewed scientific journal.

The FDA has lauded the CIR program, calling it "an important voluntary effort that should provide improved assurance to the public that the safety of cosmetic ingredients [has] been substantiated."

Dr. Karl Beyer, M.D., Ph.D., Sc.D., the first chair of the CIR Expert Panel, best captured the essence of the CIR Expert Panel when he said, "...at its inception, the term 'expert panel' related to the technical competence of its membership -- time and common cause have invested the group with a quality quite beyond their individual capabilities."

The Expert Panel has a 22 year tradition of excellence. In addition to the those individuals who served on the Panel in the past (see attachment 1), the current members of the CIR Expert Panel (see Attachment 2) continue the tradition of strong expertise, mutual reliance and respect.

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Over the past 22 years, several individuals have served as either government, industry, or consumer liaison representatives to the Panel. Representing the Consumer Federation of America have been Cathy Sulzberger, Kathleen Sheekey, Marcia Carroll, Anne Averyt, and Mary Ellen Fise.

Representatives from FDA to the Panel have included Martin Grief, John Wenninger, Heinz Eiermann, and John Bailey, Ph.D.

Industry liaisons from CTFA include James McNerney, Jack Winstead, Ph.D. and Gerald McEwen, Jr., Ph.D., J.D.

In 1993, Dr. F. Alan Andersen became the second long-term CIR Director, joining CIR after 22 years at FDA. His most recent responsibilities at FDA had been heading the medical device and radiation product testing and research laboratories, and directing the medical device evaluation unit.

By the end of 1998, CIR will have reviewed almost 800 ingredients and its findings will have been made available to the public through publication of 36 special issues of the *International Journal of Toxicology* (and its predecessor titles). As a consequence of this activity, thousands of unpublished studies have been summarized and made available to the scientific community, eliminating the need for duplicative testing.

The findings in the hundreds of CIR safety assessments have established a public record of the safety of cosmetic ingredients -- 54% of all ingredients reviewed are safe as currently used. For another 32%, CIR has established specific conditions that will allow the industry to use these ingredients safely. Where appropriate, however, ingredients considered unsafe (1%) have been identified and ingredients for which the available data are insufficient to support safety (13%) have been publicly listed.

### ***FDA'S REQUEST FOR INPUT***

As part of its efforts to implement the FDA Modernization Act, FDA has reached out to its stakeholders seeking input to a plan for complying with each of the Agency's obligations under the Federal Food, Drug, and Cosmetic Act. As outlined in FDA's message to its stakeholders, this plan is to include six objectives: maximize the availability of information about FDA's processes, ditto for information about new products, meet inspection and postmarketing obligations, ensure access to needed scientific and technical expertise, meet review time frames, and eliminate backlogs.

To help focus input to the plan, FDA has asked for responses to the following seven questions:

1. What can FDA do to improve its explanation of the Agency's submission review processes, and make explanations more available to product sponsors and other interested parties?
2. How can the Agency maximize the availability and clarity of information concerning new products?
3. How can FDA work with its partners to ensure that products -- domestic and foreign -- produced and marketed by the regulated industry are of high quality and provide necessary consumer protection; and how can FDA best establish and sustain an effective, timely, and

science-based postmarketing surveillance system for reporting, monitoring, evaluating, and correcting problems associated with use/consumption of FDA-regulated products.

4. What approach should FDA use to ensure an appropriate scientific infrastructure with continued access to scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision-making process?
5. What do you believe FDA should do to adequately meet the demands that are beginning to burden the application review process, especially for non-user fee products, so that it can meet its statutory obligations to achieve timely product reviews?
6. What suggestions do you have for the Agency to eliminate backlogs in the review process?
7. What other objectives related to the Agency's statutory obligations or public expectations -- beyond the six objectives -- should be included in the FDA plan?

While CIR is not in a position to offer comment on certain of these questions, we hope FDA will find useful the comments we are able to offer.

### ***RESPONSES TO FDA'S QUESTIONS 3, 4, and 5.***

3. *How can FDA work with its partners to ensure that products -- domestic and foreign -- produced and marketed by the regulated industry are of high quality and provide necessary consumer protection...?*

Under current FDA regulations cosmetic product manufacturers are obligated to substantiate the safety of their products. Were FDA to undertake to determine if that obligation is met, even for a few cosmetic products, each with many ingredients, the work would overtax the available resources. As can be seen from the background information provided above, CIR is in a position to carry the load of publicly implementing a safety substantiation program.

Thus, FDA has an important opportunity to work in partnership with CIR to ensure that expert, unbiased safety assessments are completed for cosmetic ingredients. Currently, FDA has a contact person who works with the CIR Expert Panel. This relationship could be made stronger with the appointment of a formal liaison representative as is done with standards developing organizations (SDOs). And as with FDA's other SDO liaison appointments, this would be based on technical expertise (in this case, in the cosmetics area) and the individual would be expected to participate fully in all scientific discussions, both in working sessions and in open, public meetings. Through such formal liaison participation, FDA can maximize its effort to address any concerns about cosmetics.

And FDA would be able honestly report to Congress that it is implementing the current regulations with a minimum expenditure of staff resources. A case in point will help illustrate this. As noted above, manufacturers are required to substantiate the safety of their products -- or if not -- a label should be provided that states that the safety has not been adequately substantiated. There are four conclusions regarding safety that have been reached by the CIR Expert Panel: safe; safe with qualifications; unsafe; and insufficient data. This last category presents opportunities for FDA, where the circumstances warrant, to use CIR conclusions as a

basis for requiring certain labeling. In an October 25, 1996 response to a citizen petition (91P-0114CP), FDA concluded that, based on the CIR Expert Panel's safety assessment of urocanic acid in which the available data were found insufficient to support safety, manufacturers would have to provide notice on labels of those products that contain urocanic acid that its safety has not been substantiated. This example shows the reliance that FDA could place on CIR conclusions in those circumstances where a concern exists. Rather than expending great Agency resources to address a question about safety substantiation, the Agency can rely on CIR's findings or, if a safety assessment has not been completed, FDA can request that one be done.

4. *What approach should FDA use to ensure an appropriate scientific infrastructure with continued access to scientific and technical expertise needed to meet its statutory obligations and strengthen its science-based decision-making process?*

That FDA does not always require among its staff all of the expertise needed to meet its obligations in house is recognized in the FDA Modernization Act itself. One of the provisions of the FDA Modernization Act calls for the recognition of conformance to voluntary standards in place of Agency staff review of performance features controlled by those standards. Such reliance is possible based on a long history of FDA participation with SDOs in a relationship where a small FDA liaison role is multiplied by orders of magnitude with the participation of scientific, medical, consumer, and industry experts.

So it is with the potential for FDA participation in CIR. CIR provides an opportunity for a small FDA investment to be multiplied by the efforts of the CIR staff to access and describe published and unpublished safety test data, and by the work of the CIR Expert Panel (see Attachment 2) to critically assess these data. Participation in the process allows FDA a significant role in identifying data needs and the kinds of studies that will be needed to generate these data.

CIR is in a position to be responsive to the needs of all parties concerned with the safety of cosmetic ingredients. Acting on a request from the CTFA in May 1994, the Expert Panel agreed to expedite the review of the most commonly used Alpha Hydroxy Acids (AHAs) because of their increased use in cosmetics. Both FDA and the Consumer Federation of America were also interested in safety data on these so-called "fruit acids," and supported the CIR action. FDA specifically expressed concern about the possibility that repeated use of AHAs would affect the barrier function of the skin, to both chemicals and ultraviolet radiation. The CIR completed its preliminary review in 1996 and its final safety assessment of AHAs in 1997 after reviewing a large amount of safety test data provided by industry and the FDA. For the first time, for example, information regarding the appropriate pH limitations of cosmetic formulations containing AHAs were available. These data formed the basis for the Expert Panel's conclusion that the pH of formulations should not be too acidic.

FDA provided the results of its own testing. FDA's data were interpreted to show that there was not a significant increase in penetration of other chemicals in animal skin treated with AHAs. Industry data in humans confirmed that finding. Industry tests of ultraviolet radiation damage in skin treated with AHAs were interpreted by the Panel as showing an increase. While industry argued that this increase was not significant compared to other activities (e.g., shaving) that affect

the skin surface, the Expert Panel concluded that it was necessary to qualify its conclusion that these ingredients can be used safely with the caveat: "when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection."

Thus, FDA's original concern about increased ultraviolet radiation damage was confirmed and action recommended which allow products containing AHAs to be used safely. This report was published in the *International Journal of Toxicology* (Volume 17, Supplement 1, 1998). Recent data describe the results of the same ultraviolet radiation skin damage testing included in the report, but with use of a product containing AHAs and a sunscreen (SPF of 4). With the addition of the sunscreen, there was no increase in ultraviolet radiation damage over controls.

This begs the question --- why didn't FDA make the proposal to CIR to review AHAs? The Agency obviously had a concern about the safety of these ingredients. While FDA supported the CIR effort once proposed by industry, FDA also expended monies to generate its own review of the literature which was less comprehensive than that done by CIR. Given the reputation and past performance of the CIR, FDA should be comfortable in recognizing the work done by CIR. And while the CIR Expert Panel had some idea of the kinds of additional data FDA considered necessary to assess the safety of AHA ingredients, FDA could have played a stronger role in listing the kinds of studies that it considered should be undertaken. And in the future, a formal FDA liaison representative to the CIR Expert Panel could have a significant impact in getting Agency concerns addressed.

5. *What do you believe FDA should do to adequately meet the demands that are beginning to burden the application review process, especially for non-user fee products, so that it can meet its statutory obligations to achieve timely product reviews?*

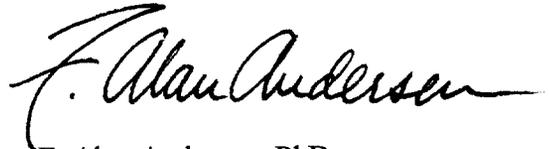
The theme that carries through the comments on the above two questions is "when someone else has it under control, don't expend FDA resources to do it." In a good example of what could be done, instead of doing costly scientific assessment and research on urocanic acid, FDA relied on CIR. An example of how not to do it, FDA paid for an "FDA" literature review of AHA ingredients, instead of relying on CIR. These two examples do not begin to reflect the potential FDA use of CIR safety assessments of what will soon be 800 cosmetic ingredients.

In each case where FDA doesn't have to do something relative to cosmetic ingredient safety substantiation because CIR is handling that, there is opportunity for resources to be used to support the other aspects of a complete cosmetics program, such as maintaining the voluntary reporting program which receives manufacturers' reports on what ingredients are used in what type of cosmetic formulations, maintaining an effective field enforcement program, and acting to promote international harmonization in the regulation of cosmetics.

Respectfully submitted,



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Chairperson, Cosmetic Ingredient Review Expert Panel  
Head of Clinical Research and Dermatopathology  
Dermatology Department  
Cleveland Clinic Foundation



F. Alan Andersen, PhD  
Director and Scientific Coordinator  
Cosmetic Ingredient Review

**First CIR Expert Panel Members**

Karl Beyer, Jr. M.D., Ph.D, Sc.D., Expert Panel Chairman, The Pennsylvania State University and the Hershey Medical Center

Wilma Bergfeld, M.D., The Cleveland Clinic Foundation

Julius Coon, Ph.D., Jefferson Medical College

Robert M. Fine, M.D., Emory University School of Medicine

Dietrich Hoffman, Ph.D., Naylor Dana Institute for Disease Prevention

William Montagna, Ph.D., Oregon Regional Primate Research Center

Robert Roudabush, Ph.D., University of Rochester School of Medicine

Martin Grief was the FDA contact person, and the liaison representatives were, Cathy Sulzberger from the Consumer Federation of America, and James McNerney from CTFA.

**Past Panel Chairs**

1977-1987 Karl Beyer, Jr., M.D., Ph.D., Sc.D., The Pennsylvania State University and Hershey Medical Center

1987-1991 William O. Berndt, Ph.D., University of Nebraska Medical Center

**Past Panel Members**

1977-1980 Robert M. Fine, M.D., Emory University School of Medicine

1977-1982 Robert Roudabush, Ph.D., University of Rochester School of Medicine

1977-1982 Julius Coon, Ph.D., M.D., Jefferson Medical College

1977-1982 William Montagna, Ph.D., Oregon Regional Primate Research Center

1977-1993 Dietrich Hoffman, Ph.D., Naylor Dana Institute for Disease Prevention

1982-1983 Jerry Hook, Ph.D., Michigan State University

1982-1984 and

1987-1993 Roswell K. Boutwell, Ph.D., University of Wisconsin

**Current CIR Expert Panel Members**

Wilma F. Bergfeld, M.D., F.A.C.P. - Chairperson, original Panel member, The Cleveland Clinic Foundation: Head of Clinical Research and Dermatopathology, Board of Governors, Cleveland Clinic Foundation. 1992 President, American Academy of Dermatology. Past Chair, Dermatology Advisory Committee, US Food and Drug Administration.

Donald V. Belsito, M.D. - Team Leader, voting member, appointed in 1991, University of Kansas Medical Center: Professor of Medicine and Director, Division of Dermatology, Diplomate of the American Board of Internal Medicine and the American Board of Dermatology.

William W. Carlton, D.V.M., Ph.D. - voting member, appointed in 1982, Purdue University School of Veterinary Medicine: Emeritus Professor of Veterinary Pathology and Toxicology, Diplomate of the American College of Veterinary Pathologists.

Curtis D. Klaassen, Ph.D. - voting member, appointed in 1993, University of Kansas Medical Center: Professor of Pharmacology and Toxicology, President, International Union of Toxicology.

Ronald C. Shank, Ph.D. - voting member, appointed in 1983, University of California-Irvine: Professor and Director of Environmental Toxicology, Former Field Director of MIT's Mycotoxin Research Program.

Arnold L. Schroeter, M.D. - Team Leader, voting member, appointed in 1980, The Mayo Clinic: Professor and Chair of Dermatology, Past Chair, Dermatology Advisory Committee, U.S. Food and Drug Administration.

Thomas J. Slaga, Ph.D. - voting member, appointed in 1993, University of Texas M.D. Anderson Cancer Center: Director and Professor of Carcinogenesis, Editor-in-Chief of the journal, "Molecular Carcinogenesis."

John E. Bailey, Ph.D. - FDA Contact Person, U.S. Food and Drug Administration, Washington, D.C., Director, Office of Cosmetics and Colors

Mary Ellen Fise, Esq. - Consumer Liaison, Consumer Federation of America, Washington, D.C.: General Counsel

Gerald N. McEwen, Ph.D., J.D. - Industry Liaison, The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C., Vice President, Science.

F. Alan Andersen, Ph.D. - Director and Scientific Coordinator, Cosmetic Ingredient Review