1
Cosmeceuticals: Do We Need a New Category?

Albert M. Kligman
University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

I introduced the term cosmeceuticals almost 20 years ago at a meeting of the Society of Cosmetic Chemists. I thought this neologism was both timely and useful, since it would reconcile archaic legal statutes with modern science.

I anticipated immediate endorsement of a concept whose time had come. Instead, the response was immediate disapproval and denouncement. My colleagues in the industry branded me a troublemaker, unfaithful to those who had supported my research. Since then, the cosmeceutical concept has generated a huge amount of controversy. Along the way, the term has acquired political, economic, and legal connotations that have further obscured the intended purpose of the idea.

Whether one is pro or con, the term cosmeceutical has permanently entered the vocabulary of skin care science. For some, the term has been transformed into a marketing tool, touting the benefits of skin care products. Others see it as a provocation for unwanted, costly, regulatory actions. The most benign view is that the category is superfluous and has no raison d'etre. Cosmeceuticals seem to have a certain semantic resonance, as witnessed by similar sounding neologisms; for example, neutraceuticals (foods with health benefits) and neoceuticals (over-the-counter drugs with cosmetic effects).

In any case, the term is here to stay and has provoked lively debates that, in the end, may strengthen our understanding of the science of cosmetics. I think it will be informative to review the history of this curious case.

I present the unfolding story from the viewpoint of an investigative dermatologist who appreciates the tremendous technical strides made by the cosmetic industry in recent times.

Interest in cosmeceuticals has rushed forward at an impressive pace. Seminars entitled ''Cosmeceuticals'' are being staged annually. These forums are well attended by groups having widely different backgrounds and interests (regulators, basic scientists, physicians, manufacturers, publishers, merchandisers, lawyers, toxicologists, pharmacologists, and industry watchers). Papers and books have been written covering every aspect of the subject, and these provide a rich source of information (1).

Cosmeceuticals are a hot topic on an international scale. The literature has expanded rapidly, presenting a great variety of views dictated by special interests. A number of forces have converged to power this surge of interest. It would seem that some merchandisers have realized the potential for increasing the sale of products that go well beyond the traditional view of cosmetics as merely decorative or camouflaging. Skin care products can now be viewed as active they do something useful and beneficial. They contain ''bioactives'' which, though not medicinal, are endowed with functional and measurable attributes. Alternative terms for cosmeceuticals have sprung up (performance cosmetics, functional cosmetics, dermoceuticals, active cosmetics). All these imply value added desirable attributes, the touchstone for success in a wildly competitive marketplace.

This is a marketer's playground, which makes it possible to incorporate in skin care products an unlimited number of active substances from natural sources (plants, the sea, the earth). The list of beckoning substances, including those synthesized by chemists, is staggering, including vitamins, antioxidants, anti-inflammatories, mood-influencing fragrances (aromatherapy), and even such exotica as placenta, amniotic fluid serum, and hormones ad infinitum. The choices range from the preposterous to the persuasive, and cover the spectrum from the irrational to the rational.

The natural and green movements also provide a background for understanding the robust interest in cosmeceuticals. For many uninformed consumers, natural is good and synthetic is bad; green protects the environment and prevents cruelty to animals. The phrases, ''not tested on animals'' and ''cruelty-free'' have become a marketing ploy that is often hypocritical and false. Marketers understand these lofty impulses of consumers and are quite willing to cater to the widespread prejudices of a chemophobic population. However, cosmeceuticals are here to stay because they serve the multiple needs of manufacturers and consumers.

THE 1938 FOOD, DRUG, AND COSMETIC ACT: THE BEGINNING OF TROUBLE

In 1938, the U.S. Congress enacted a statue that officially defined cosmetics and drugs in detailed terms, setting up formal criteria for classifying a product as either a drug or a cosmetic. No intermediate category exists, although it was appreciated that a topical could be both a cosmetic and a drug at the same time. This remains the law to this very day.

The 1938 act came into being as a corrective reaction against the ludicrous number of elixirs and patent medicines—some dangerous—which promised cures for all human ailments. It defined a cosmetic, in pertinent part, as an ''article intended for beautifying and promoting attractiveness.'' In contrast, a drug was defined as a substance for use in the diagnosis, cure, treatment, or prevention of disease, *intended to affect the structure and function of the body*. This last clause legally determines whether a formulation is a drug or a cosmetic. It is this narrow phrase that prompted me to coin the term cosmeceutical.

It is important to note that it is not the ingredients in a product, but the claims in labeling or advertising, that determine whether the substance will be classified as a cosmetic or a drug. Congress also declared that the ''intended'' use would determine a product's classification. Thus, if the intended use relates to the diagnosis and treatment of a disease, the substance is a drug; if its intended use is described in advertisements as promoting attractiveness, the substance is a cosmetic. Thus, in reality, you are what you claim you are.

ENTER COSMECEUTICALS

When the 1938 law was written, the science of cosmetology was primitive and crude, steeped in folklore and unsupported claims. The 1938 definition of a drug is now completely archaic and, in fact, an oxymoron. With the great advances in our understanding of skin physiology, it is impossible to think of a single substance that cannot, under some circumstances, alter the structure and function of skin. The most compelling example is water, the milieu in which all vital processes occur which is considered innocuous. However, when a water-moistened cotton pad is sealed to human skin for 2 days, proinflammatory substances such as interleukins are released from the dead stratum corneum. These incite a series of cytotoxic changes in the viable epidermis below (2). In another few days, an inflammatory reaction is provoked in the dermis. This is the basis for the adverse clinical events associated with prolonged exposure to water, for example, in bartenders, housewives, canners, etc. Thus water can be beneficial in emulsions that hydrate xerotic skin or harmful under intensive exposure.

Another traditional substance considered inert is petrolatum. However, various studies show that petrolatum promotes healing of wounds and prevents ultraviolet-induced tumors, even though it is not a sunscreen (3). These are clearly medicinal effects that affect the structure and function of skin, yet no rational person would want petrolatum to be reclassified as a drug. From these and many other examples, it is apparent that nearly all cosmetic articles would have be be reclassified as drugs, if a strict interpretation of the ''structure and function'' proviso of the 1938 act were used.

Most skin care products lie somewhere in between drugs and cosmetics. They comprise a continuous spectrum of substances intermediate between the two polar categories defined by Congress. Some traditional cosmetics are more druglike in their beneficial effects and some drugs impact principally on appearance. It is this intermediate, broad-spectrum range of substances that consists of both drugs and cosmetics which justifies the fusion term cosmeceuticals. This is simply a biological concept that recognizes the new realities of skin care products.

This acceptance of biological reality does not mean that we need new laws that officially define in statutory terms the category of cosmeceuticals. The FDA has always had the authority to determine from advertising claims and labeling whether a product promoted as a cosmetic has crossed the line and requires reclassification as a drug.

Cosmeceutical is a pragmatic term that enables us to state without pretense the benefits of a product. It is not an invitation to pass new laws.

A strict, legal interpretation of the 1938 law would necessitate the conversion of ''active'' cosmetics to drugs. This would be a disaster of the highest magnitude that would immediately stifle innovation and creativity. Drug development is slow and costly, and requires proof of efficacy and safety. Cosmetics, on the other hand, do not require premarketing clearance and can be rapidly commercialized provided that the claims are not grossly misleading.

Over the years, and to its credit, the FDA has been flexible and permissive in the way in which it has viewed claims, some of which are unequivocally exaggerated. The trouble comes when some cosmetic manufacturers make frank drug claims for their products. In this case, the FDA sends out warning letters that require relabeling of the products without necessarily changing any of the ingredients. Competitors who are prudent and conscientious may be at a disadvantage if they make less aggressive claims, an issue highlighted by the ''antiaging'' claims made for certain α-hydroxy acids.

Cosmeceuticals enable cosmetic scientists to communicate with each other regarding the standards that must be met to justify performance claims, without resorting to hype.

THE INTERNATIONAL SCENE

There are three main trading blocks, the United States, Europe, and Japan. Obviously globalization as an integrated free-trade network cannot work if each block classifies and regulates skin care products differently. Unfortunately, no international consensus currently exists, inevitably sparking disputes and trade practices that may place some producers at a grave disadvantage.

The situation is more complex and far more demanding in Europe. This is made obvious in the European Economic Cosmetic (EEC) Directive of 1993. The requirements for labeling cosmetics are formidable and daunting (4). The product information that must be made available to officials encompasses the following: qualitative and quantitative composition of the product: specifications of raw materials; methods of manufacture; safety assessments; and proof of effectiveness. In the United States, manufacturers are not required to demonstrate either safety or efficacy prior to marketing, as is the case for drugs. On top of all this, the EEC has prohibited testing on animals after January 1998 (which I judge to be completely unrealistic).

Japanese authorities have created their own laws in response to the problem that many skin care products are neither pure drugs nor pure cosmetics in the traditional sense, but mixtures of the two. The category we call cosmeceuticals they call quasidrugs (5). They allow cosmetics to include pharmacologically active ingredients, provided that the medicinal effects are mild and the products have been demonstrated to be safe. The legal wording leaves a lot of room for ambiguities and ad hoc interpretations that some perceive as a trade restraint.

Even a cursory look at these regulatory disparities shows the detrimental effects of not establishing uniform, international standards. The following examples illustrate the quandaries which now exist, a situation which is bound to get nasty without an international consensus.

In the United States, the following agents are regulated as drugs while in Europe (according to the European commission on cosmetics) they are sold as cosmetics.

1. Antiperspirants
2. Antidandruff shampoos
3. Sunscreens

This classification is detrimental to industry in the United States, especially in the case of sunscreens, which are more advanced and more effective in Europe because there is greater choice of ingredients. Paradoxes also abound in the United States. For example, retinol (vitamin A) can be sold as a cosmetic, but its oxidation product, retinoic acid, is regulated as a drug. Furthermore, claims

allowed by the FDA for a recently approved retinoic acid product (Renova, Ortho Pharmaceuticals) are purely cosmetic and relate only to improved appearance. However, the product is still only available by prescription!

On the other hand, minoxidil, a drug that purports to grow hair and improve attractiveness, satisfies the basic definition of a cosmetic and is available without a prescription.

Sometimes, there are too many statutory exceptions and loopholes that are downright dangerous. For example, theophyllin is a powerful drug with a narrow therapeutic index, and is used in the treatment of asthma; blood levels should be monitored frequently. Yet, this same agent can be sold as an unregulated cosmetic when incorporated in topical formulations for the treatment of cellulite.

I recommend that all interested parties read the scholarly treatise prepared by Vermier and Gilchrest, respectively (6). They argue that cosmeceuticals already exist and are in fact desirable as intermediates between cosmetics and drugs and that they should continue to be regarded as cosmetics. The current legal definitions are archaic and unworkable. They move toward the European position and recommend that it is in the interest of manufacturers to prove the efficacy of active cosmetics.

COSMECEUTICALS: A DIVERSITY OF OPINIONS

The writings on this subject are fascinating and cover a remarkable range of divergent, confusing, and conflicting opinions from all over the globe (7). Recent papers strongly express the feelings and beliefs of major players in this field.

Dweck's paper provides the British perspective. He begins as follows: What on earth is a cosmeceutical (8)? Is it an attempt to convince the consumer that their skin care product is really a topical medicine without a proper license, or is it a genuine category that attempts to provide a mild product that has been more stringently tested than a normal skin care product? He recommends reading an official medicine leaflet as a guide to deciding what comprises a medicinal product. He concludes that future discussions will be marked by debate. The British have clearly reached no conclusions.

Wittern takes up the issue from a European perspective. He is decidedly not enamored of the term cosmeceutical (9). He considers ''that the existing legal regulations are precise and clearly distinguish between cosmetic and pharmaceutical efficacy. They do not allow for the introduction of a new class of products such as cosmeceuticals.'' He recounts that A. M. Kligman introduced the term but didn't bother to define it. ''Obviously, he didn't know what he was starting.'' I plead guilty to not knowing what controversial storms would follow the concept. The piece de resistance of the cosmeceutical imbroglio is the article by Urbach (10), who states:

> At the moment, there is hardly a topic in the cosmetic industry as controversial as cosmeceuticals . . . Cosmeceuticals meet consumer demands for high efficacy. From a consumer and regulatory point of view, having a separate cosmeceutical class in neither helpful, scientifically suitable or juridically necessary. The cosmeceutical concept is superfluous. The most sensible and useful service we can give the consumer legislator and manufacturer is to advise against the further use of this term (11)!

Steinberg presents the American perspective (11). He endorses the term and thinks its introduction has made it necessary to reconsider the statutory definition of a drug and a cosmetic and to seek international agreements on the kinds of regulatory actions that might be enacted.

The situation is quite different in Japan, as described by Takamatsu (5). It turns out that the Japanese government recognized early on the problems that were coming to the fore as a result of the cosmetic industry's ability to create ''performance'' products that did more than beautify.

It is abundantly clear that, for the sake of fair trade, a rapidly expanding international marketplace will have to come to grips with the problems presented herein.

REFERENCES

1. Hayward JA. Biotechnology transfer. Cosmet Toilet 1995; 110:51.
2. Kligman AM. Hydration injury to human skin. In: Van der Valk PGM, Maibach HI, eds. The Irritant Contact Dermatitis Syndrome. Boca Raton: CRC Press Inc., 1996:187–194.
3. Kligman LH, Kligman AM. Petrolatum and other hydrophobic emollients reduce UVA-induced damage. J Dermatol Treatment 1992; 3:3.
4. Rogiers V. Efficacy claims of cosmetics in Europe must be scientifically substantiated from 1997 on. Skin Res Technol 1995; 1:44.
5. Takamatsu T. How can we define cosmeceuticals. Advanced Technology Conference Proceedings. Cosmetics Toiletries. Carol Stream, IL: Allured Publishing Co., 1996: 30.
6. Vermier BJ, Gilchrest BA. Cosmeceuticals. A proposal for rational definition, evaluation and regulation. Arch Dermatol 1996; 132:337.
7. Kligman AM. Why cosmeceuticals? Cosmet Toilet 1993; 108:39.
8. Dwek AC. The definition of a cosmeceutical. Advanced Technology Conference Proceedings. Cosmetics Toiletries. Carol Stream, IL: Allured Publishing Co., 1996:21.
9. Wittern KP. Cosmeceutical from a European perspective. Cosmetics Toiletries. Advanced Technology Conference Proceedings, Cosmetics Toiletries. Carol Stream, IL: Allured Publishing Co., 1996:24.
10. Urbach W. Cosmeceuticals—The future of cosmetics? Cosmet Toilet 1995; 110:33.
11. Steinberg D. An American Perspective. Advanced Technology Conference Proceedings. Cosmetics Toiletries. Carol Stream, IL: Allured Publishing Co., 1996:26.

2
Definition

Bert Jan Vermeer
Leiden University Medical Center, Leiden, The Netherlands

New insights about the function of the skin, as well as the development of new products for skin care, make it necessary to question or redefine the definitions of cosmetics and drugs. Moreover, in the United States, Europe, and Japan, different definitions of cosmetics are used. The definition of a drug is more or less equivocal on these countries. According to the Food, Drug, and Cosmetic (FDC) Act, a drug is defined as an article intended for use in the diagnosis, mitigation, treatment, or prevention of disease or intended to affect the structure or any function of the body.

In the United States, according to the FDC act of 1938, a cosmetic is defined as an article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance without affecting structure or function (1). It is noteworthy that in this definition the cosmetic is not allowed to have any activity (i.e., without affecting structure or function). In Europe, the definition of a cosmetic was reevaluated and described by the council directive 93/35/EEC of June 14th, 1993 (2). The cosmetics directive contains 15 articles. The definition of a cosmetic is described in article 1 and is as follows:

> A ''cosmetic product'' shall mean any substance or preparation intended to be placed in contact with the various external parts of the human body epider-

> mis, hair system, nails, lips and external genital organs or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition.

The other 15 articles describe the following topics: overall safety requirements, controlled substances, potential ban of animal testing, inventory of ingredients, labeling, harmonization, product information requirement, procedure for adaptation, list of permitted ingredients, safeguard clause, and implementation.

According to the pharmaceutical affairs law, the Japanese definition of a cosmetic is as follows:

> The term cosmetic means any article intended to be used by means of rubbing, sprinkling or by similar application to the human body for cleansing, beautifying, promoting attractiveness and altering appearance of the human body, and for keeping the skin and hair healthy, provided that the action of the article on the human body is mild.

The Japanese definition is only slightly different from the definition of a cosmetic within Europe. Both definitions allow a cosmetic to have mild activity and possess pharmaceutical activity. This is in sharp contrast to the definition of a cosmetic in the United States.

Moreover, in article 7a of the European cosmetics directive, which describes the product information requirement, it is stated that a proof of effect should be included (2). In the United States, however, a product would be regarded as a drug if a proof of effect was mentioned.

Extensive research on the physiological activity of the skin has provided evidence that even small changes in the environment can modify the activity of skin tissue (3,4). Application of inert creams (5), humidity, UV light (4), water (6), etc., all influence the activity of the skin and therefore possess pharmaceutical activity that may affect structure or function of the skin. Thus even water or the humidity of the air could be defined as a drug, according to the FDC act! As mentioned by Gilchrest, the Food and Drug Administration asked her to define water as a drug, when water was applied on the skin under experimental conditions (7).

Registration of a product as a drug requires many elaborate and costly procedures; therefore, the manufacturer of a product with pharmaceutical activity would prefer to have the product registered as a cosmetic. This might mean that the pharmaceutical activity of the product is not mentioned and/or investigated, and, as a result of these confusing and old-fashioned regulatory rules, important information is not given to the public.

The introduction of the term ''cosmeceutical'' enables us to classify more precisely a product with an activity that is *intended* to treat or prevent a (mild) skin (abnormality). In order to avoid introducing new definition criteria, we suggest that cosmeceuticals are only regarded as a subclass within the domain of a

Table 1 Cosmeceuticals as a Subclass of Cosmetics (Europe and Japan) and as a Subclass of Drugs (U.S.)

	Cosmetic	Cosmeceutical	Drug
Pharmaceutical activity	+	+	+
Intended effect in skin disease	−	(+)	+
Intended effect in mild skin disorder	−	+	(+)
Side effects	−	(±)	+

cosmetic or drug. In Europe and Japan, cosmeceuticals can be regarded as a subclass of cosmetics; however, in the United States cosmeceuticals can only be regarded as a subclass of drugs. Cosmeceuticals could be characterized as follows: (1) The product has pharmaceutical activity and can be used on normal or near-normal skin. (2) The product should have a defined benefit for minor skin disorders (cosmetic indication). (3) As the skin disorder is mild the product should have a very low-risk profile (see Table 1). The definition of minor skin disorders or mild skin abnormalities is difficult and can be regarded as cosmetic indications. Even socioeconomic factors may have an impact on whether a skin disorder is regarded as a disease or as a cosmetic indication (8,9). Nevertheless, in most western countries there is no written consensus that skin abnormalities that are treated by over-the-counter drugs may be regarded as mild skin disorders or may be termed cosmetic indications (9,10).

The procedure for registration of a cosmeceutical should not be as cumbersome as for drugs. The intended activity of the cosmeceutical for treatment of a minor skin disorder should be demonstrated by clinical studies within the framework of good clinical practice. Moreover, it should be shown that safety requirements are optimal and that no side effects can be expected (11). The safety evaluation is mandatory for cosmetics in Europe, according to articles 2, 12, and 13.

In the United States, this would mean that a subclass of drugs (cosmeceuticals) are registered in a similar manner as over-the-counter products (12). It would be beneficial if these countries could agree on the definitions of cosmetics and drugs and, in so doing, define cosmeceuticals as a subclass of cosmetics. This would prevent the current situation in which certain products are registered as drugs in the United States (sunscreens) and as cosmetics or cosmeceuticals in Europe and Japan.

REFERENCES

1. 21 USC §§ 301–393.
2. Council directive 78/768 EEC of july 27th, 1976. Official Journal of the European Communities n° L 151 dated June 23rd, 1993.

3. Lundström A, Egelrud T. Evidence that cell shedding from plantar stratum corneum in vitro involves endogenous proteolysis of desmosomal protein desmogein. J Invest Dermatol 1990; 94:216–220.
4. Noonan FP, De Fabo EC. Immunosuppression by ultraviolet B radiation, initiation by urocanic acid. Immunol Today 1992; 7:250–254.
5. Mertz PM, Davis SC, Ovington LG. Cosmeceuticals: predicting their influence on compromised skin. Cosmet Toilet 1992; 107:43–44.
6. Harris JR, Farrel AM, Grunfeld C, Holleram WM, Elias PM, Feingold KR. Permeability barrier disruption coordinately regulates RNA levels for key enzymes or cholesterol, fatty acid and ceramide synthesis in the epidermis. J Invest Dermatol 1997; 109:783–788.
7. Vermeer BJ, Gilchrest BA. Cosmeceuticals. Arch Dermatol 1996; 132:337–340.
8. O'Donoughue MN. Sunscreen: the ultimate cosmetic. Dermatol Clin 1991; 9:99–104.
9. Neher JO. Cosmetics by prescription. J Fam Pract 1989; 29:534–536.
10. Nightingale SL. FDA proposes new labeling for over-the-counter sunscreen products. JAMA 1992; 270–302.
11. Stern RS. Drug promotion for an unlabeled indication: the case of topical tretinoin. N Engl J Med 1994; 331:1348–1349.
12. De Salva SJ. Safety evaluation of over-the-counter products. Regul Toxicol Pharmacol 1985; 5:101–108.