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Cosmetology, Cosmetics, Cosmeceuticals: Definitions and Regulations

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The growth of the cosmetic industry, together with the dramatic increase in advances in cosmetic chemistry, has been one of increasing interface with dermatologists. The change especially in dermatology has found less emphasis on medical dermatology and growth in the areas of cosmetic dermatology and dermatologic surgery. With this, the dermatologist has had to become more aware of principles and products in the field of cosmetics. The use of these newer products as an adjunct to the practice of dermatology coincides nicely with recent international congresses, whose theme has been "healthy skin for all" and variations on such.

Perhaps the major body for the oversight of this growth remains the U.S. Food and Drug Administration (FDA), which for many parts of the world provides the assurance of safety and quality for various foods, drugs, and cosmetics. The mandate for much current regulation and oversight began in 1938 with the Food, Drug, and Cosmetic Act, which placed active oversight on various drugs and cosmetics and was further modified in 1960 by the Delaney Amendment, which focused on the growing awareness of carcinogenic potential of various agents, topical and systemic.[1] Since the radium scare of the 1920s and 1930s, the increasing use of synthetic materials has focused on delayed long-term potential cancer risks and health hazards. More recently, such agents as Dioxin, Agent Orange, and certain other fungicides and pesticides have seemingly justified this new role of the FDA. Of particular confusion at the present time are certain dyes—FD&C Red #3, FD&C Yellow #5, hair dyes—and other agents that are essential in the cosmetic and "cosmeceutical" practice. The variability of interpretation of safety still confounds easy interpretation of the administration's role in the approval of new uses, particularly in the cosmeceutical area. At the present time, FD&C Red #3 has been banned for provisional usages, and there has been expanded oversight on tartrazine, or FD&C Yellow #5.

Simply put, according to the FDA, drugs are defined as "products that cure, treat, mitigate or prevent disease, or that effect the structure or function of the human body." The identification of a particular agent as fitting these categories changes the process in the United States of FDA oversight. The cosmetic industry is continually on the edge of this area, making subtle claims of certain additives (Retinol, for example) that purport to effect the structure of the human body. In the case of Retinol, which has been shown to penetrate the epidermis,[2] this interpretation is that regular usage will provide antioxidant properties for the skin, retarding the aging process. Such claims should initiate a careful review by the FDA. Even when such claims (often verbal or made in newspapers, rather than distributed through scientific channels) are made, that they rarely change the FDA requirements on such products. This usually has not been the case because the volume of new products exceeds the FDA's ability to review and/or regulate. The FDA does not accept or define the term "cosmeceutical", whereas nearly universally around the world this has become the new phrase (catch-word) for the millennium change in cosmetics to retard aging. Kligman offers this guidance in a dermatologist's evaluation of new cosmeceuticals:

1. Can the active ingredient penetrate the stratum corneum and be delivered in sufficient concentrations to its intended target in the skin over a time course consistent with its mechanism of action?
2. Does the active ingredient have a specific biochemical mechanisms of action in the target cell or tissue in human skin?
3. Are there published, peer-reviewed, double blinded, placebo-controlled, statistically significant clinical trails to substantiate the efficacy claims?[3]

Over the last 30 years, the increasing use of "natural" products and the return to alternative medicine, further complicates the issues.[4] "Natural products" superficially would seem to be synonymous with "safe" products. Specific definition of "natural" in pharmaceuticals is as nebulous as "organic" in foods. Many poisonous

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Table 1. Ingredients Prohibited or Restricted by Regulation

Regulations specifically prohibit or restrict the use of the following ingredients in cosmetics. For complete details, refer to the relevant regulations (21 CFR, Parts 250.250 and 700.11 through 700.23):

Hexachlorophene	Because of its neurotoxic effect and ability to penetrate human skin, hexachlorophene (HCP) may be used only when an alternative preservative has not been shown to be as effective. The HCP concentration of the cosmetic may not exceed 0.1%, and it may not be used in cosmetics that in normal use may be applied to mucous membranes, such as the lips.
Mercury compounds	Mercury compounds are readily absorbed through the skin on topical application and tend to accumulate in the body. They may cause allergic reactions, skin irritation, or neurotoxic manifestations. The use of mercury compounds as cosmetic ingredients is limited to eye area cosmetics at concentrations not exceeding 65 parts per million (0.0065%) of mercury calculated as the metal (about 100 ppm or 0.01% phenylmercuric acetate or nitrate) and provided no other effective and safe preservative is available for use. All other cosmetics containing mercury are adulterated and subject to regulatory action unless it occurs in a trace amount of less than 1 part per million (0.0001%) calculated as the metal and its presence is unavoidable under conditions of good manufacturing practice.
Chlorofluorocarbon propellants	The use of chlorofluorocarbon propellants (fully halogenated chlorofluoroalkanes) in cosmetic aerosol products intended for domestic consumption is prohibited.
Bithionol	Because it may cause photo-contact sensitization.
Halogenated salicylanilides (di-, tri-, metabromsalan, and tetrachlorosalicylanilide)	Because they may cause photocontact sensitization.
Chloroform	Because of its animal carcinogenicity and likely hazard to human health.
Vinyl chloride	As an ingredient of aerosol products, because of its carcinogenicity.
Zirconium-containing complexes	In aerosol cosmetic products, because of their toxic effect on lungs, including the formation of granulomas.
Methylene chloride	Because of its animal carcinogenicity and likely hazard to human health.

Adapted from: U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Cosmetics Fact Sheet, "Prohibited Ingredients and Related Safety Issues," http://vm.cfsan.fda.gov/~dms/cos-210.html.

alkaloids, for instance, are natural products. So "safe" and/or "effective" are not synonymous with such an appellation.

The recent world congresses of the International Academy of Cosmetic Dermatology, and the growth of cosmetic dermatology societies in most regions around the world, have highlighted the increase in dermatologists' involvement in these areas. It is pertinent for dermatologists to be aware of the FDA's position in that an increasing number of dermatologists are compounding products purported to function with antioxidant properties to retard ageing or improve cosmesis for patients. Traditionally, the role of the physician, after determining the root cause of the medical condition and then preparing appropriate treatments using a compounding pharmacist, has now diminished to the point where compounding is nearly all the time the domain of dermatologists. Extension of simple compounding of various products to the area of cosmetics or cosmeceuticals has been natural, and a growth area for many dermatologists in practice. The limitations of the role of the FDA is this area is clearly described in the FDA cosmetics fact sheet.[5] While the FDA does not have the authority to approve cosmetic products' ingredients, except the above-mentioned color additives, there are several federal regulations prohibiting certain ingredients found in Title XXI of the Code of Federal Regulations, Parts 250.250 and 700.11 through 700.23. The agents that are specifically prohibited or usage restricted are seen in Table 1. It is worthwhile to note that the current aggressive usage of antioxidants does not involve any of these agents that are regulated by the FDA, but has highlighted the problem of occasional contact dermatitis with some of these natural products compounded even by large cosmetic or pharmaceutical companies. The most recent example has been vitamin E, which created a significant increase in contact dermatitis in the 1970s when it was added to many cosmetic and deodorant products, much in the same manner that retinol is today. Additionally, the CTFA (Cosmetic Toiletry and Fragrance Association) has established the Cosmetic Ingredient Review (CIR) expert panel, which has listed additional agents unsafe, including the antioxidant P-hydroxyanisole, which can cause skin pigmentation, and several other agents (see Table 2) that have potential for carcinogenicity. As one can see, the regulation or prohibition in the cosmetic and cosmeceutical world, as listed on Tables 1 and 2, represents a very small number of products.

Regulation is further complicated by modification of cosmetics and cosmeceuticals with colors for masking of consumer acceptance (Table 3) and other agents to prevent contamination. Contamination can occur as a by-product of the manufacturing process, resulting in agents formed, such as nitrosamine and dioxane, that have potential health risks, Contamination can occur with the repeated use of topical agents on the skin, and oxidation of the product or microbial contamination can then lead to allergenicity, carcinogenicity, or infection. The prevention of oxidation and microbial contamina-

Table 2. Unsafe Ingredients in Cosmetics

Chloroacetamide (a preservative)	Because of sensitization (development of allergic reactions).
Ethoxyethanol and Ethoxyethanol Acetate (a solvent)	Because of reproductive and developmental toxicity.
HC Blue No. 1 (a hair coloring ingredient)	Because of possible carcinogenicity.
p-Hydroxyanisole (an antioxidant)	Because of skin depigmentation.
4-Methoxy-m-Phenylenediamine, 4-Methoxy-m-Phenylenediamine HCl, and 4-Methoxy-m-Phenylenediamine Sulfate (hair dye ingredients)	Because of possible of carcinogenicity.
Pyrocatechol (used in hair dyes and skin care preparations)	Because of carcinogenic and co-carcinogenic potential (CIR describes this substance as unsafe for leave-on products and considers available data insufficient to assure safety for use in hair dyes).

Adapted from: 1999 CIR Annual Report, cited by U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Cosmetics Fact Sheet, "Prohibited Ingredients and Related Safety Issues," http://vm.cfsan.fda.gov/~dms/cos-210.html.

tion is often the area where cosmetic chemists add various antioxidants and other preservatives to the product, some of which until recently have not claimed benefit other than prevention of degradation of the product by rancidification and other means. This would improve the stability and shelf life of the products, as well as help retard microbial contamination. One has only to look at the commonly used True-Test series of contact dermatitis patch tests to see the significance of many of these additives in the area of contact dermatitis (see Table 4).

Further, over the years, the antimicrobial aspects of certain additives led to widespread use and allergenicity or photo-allergenicity and other forms of toxicity, which ultimately resulted in these agents, (e.g., hexachlorophene, bithionol, halogenated salicylanilides, and salicylanilides) being banned from usage (see Table 1).

Other Definitions

Fragrances/Fragrance Free

The last area of concern, which also is out of the realm of usual oversight in most countries, has been the problem of sensitivity to fragrances.[6] Fragrances may indeed be merely masking fragrances, while others are very desirable for the consumer, for instance in perfumes such as Shalimar with the photosensitizer oil of bergamot. Fragrance sensitivity is a challenge to the dermatologist specializing in sensitivity to drugs and cosmetics.[7] While the patient with sensitive skin is advised to seek certain key identifiers, these have no official recognition or labeling requirements, and therefore may vary from product to product but nonetheless remain the only way to guide our patients for safety's sake. It is worthwhile noting that a label of "fragrance-free" identifies products that seem to lack any actual fragrance, but indeed may have the masking fragrances to get rid of unpleasant odors in the product as it is compounded.

Similarly, hypoallergenic products do not guarantee total freedom from allergic reactions, but are certainly important in the allergic patient's awareness if cosmetics are deemed important in spite of a high level of sensitivity. For the acne prone patients, noncomedogenic similarly has validity but no official status, and sometimes the testing with rabbit ears is the hallmark for this claim but not always.

Cosmetic products in nail care represent another area of cosmeceuticals that are a significant cause of cutaneous problems that are outside of the FDA's close scruitingy.[8]

Table 3. Color Additive Terms

Allura Red AC	The common name for uncertified FD&C Red No. 40
Certifiable Color Additives	Colors manufactured from petroleum and coal sources listed in the Code of Federal Regulations for use in foods, drugs, cosmetics, and medical devices
Coal-Tar Dyes	Coloring agents originally derived from coal sources
D&C	A prefix designating that a certifiable color has been approved for use in drugs and cosmetics
Erythrosine	The common name of FD&C Red No. 3
Exempt Color Additives	Colors derived primarily from plant, animal, and mineral (other than coal and petroleum) sources that are exempt from FDA certification
Ext. D&C	A prefix designating that a certifiable color may be used only in externally applied drugs and cosmetics
FD&C	A prefix designating that a certified color can be used in foods, drugs or cosmetics
Indigotine	The common name for uncertified FD&C Blue No. 2
Lakes	Water-insoluble forms of certifiable colors that are more stable than straight dyes and ideal for product in which leaching of the color is undesirable (coated tablets and hard candies, for example)
Permanent Listing	A list of allowable colors determined by tests to be safe for human consumption under regulatory provisions

Adapted from: U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Cosmetics Fact Sheet, "Color Additives," http://vm.cfsan.fda.gov/~dms/cos-221.html.

Table 4. Allergen Components from True Test Kit

Allergen Components on T.R.U.E. TEST Panel 1.1	*Allergen Components on T.R.U.E. TEST Panel 2.1*
1. Nickel sulfate	13. p-tert-Butylphenol formaldehyde resin
2. Wool alcohols	14. Epoxy resin
3. Neomycin sulfate	15. Carba mix
4. Potassium dichromate	16. Black rubber mix
5. Caine mix	17. Cl+Me− Isothiazolinone
6. Fragrance mix	18. Quaternium-15
7. Colophony	19. Mercaptobenzothiazole
8. Paraben mix	20. p-Phenylenediamine
9. Negative control	21. Formaldehyde
10. Balsam of Peru	22. Mercapto mix
11. Ethylenediamine dihydrochloride	23. Thimerosal
12. Cobalt dichloride	24. Thiuram mix

Natural

It also should be noted that, as mentioned previously, natural products are not synonymous with safety, and indeed, being the opposite of synthetically produced products, they may have a greater variability in content. Pure chemical compounding can significantly minimize contamination, whereas making products from natural sources can never totally have batch-to-batch consistency, and biologic additives can cause problems for the patient.

The last, and most important definition/dictum remains caveat emptor!

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