Cosmeceuticals: myths and misconceptions

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Abstract Cosmeceuticals, or physiologically active cosmetics, are subject to many misconceptions. Most consumers mistakenly believe that cosmeceuticals are regulated and tested as drugs. They also believe that the ingredients and final products have been tested for safety and that the claims made in advertisements are valid. Although cosmeceuticals and pharmaceutical ingredients have never been closer together, their regulatory environments are vastly different due to the distinct Congressional mandates given the Food and Drug Administration. Physicians are in a good position to help patients and potential cosmeceutical users understand the benefits and realistic limitations of these products.

No market regulated by the United States (U.S.) Food and Drug Administration (FDA) is more affected by fashion and whim than the cosmetic industry. The cosmetic market is big business, responsible for billions of dollars of consumer spending in the United States alone.¹ It is subject to myths and misconceptions, in part because of aggressive and competitive marketing tactics. Implied claims of potency and effectiveness can easily mislead the consumer and professional, alike.

The term “cosmeceutical” was coined in 1961 by Raymond Reed, founding member of the U.S. Society of Cosmetic Chemists.² He originally conceived the word to describe “active” and science-based cosmetics. The word and concept were further popularized by Dr Albert Kligman in the late 1970s, with the development of prescription-strength tretinoin for the enhanced appearance of ultraviolet (UV) damaged and wrinkled skin. Common usage has expanded the definition to include “a cosmetic that has or is purported to have medicinal properties.” The cosmetic industry uses the term to indicate those products that affect the health of skin or that have a sustained effect on the skin’s appearance beyond the time of application. These definitions imply a physiologic or pharmacologic action.

With the exception of tretinoin and tazarotene the products in this class are sold over-the-counter (OTC) and are regulated as cosmetics, not pharmaceuticals. The government does not recognize a separate “cosmeceutical” category. This fact affects the type of product testing done, the format and substantiation of claims, and the language used in promotion of the products. Lack of awareness of this important issue among physicians, skin care professionals, and consumers has led to many misunderstandings about cosmeceuticals.

Some of the most common myths and misconceptions, all of which are false, are:

- Cosmeceuticals and cosmetics are regulated as drugs.
- Cosmeceutical claims in labeling and advertising are substantiated and approved before market.
- Cosmetic ingredients undergo premarket testing and review by the FDA for safety.
- Cosmetic ingredients undergo premarket testing and review by the FDA for efficacy.
- “Natural” products are safer than synthetic.
- “Cruelty-free cosmetics” have had no animal testing, and are a special noble movement.

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Hypoallergenic means that the product has been tested to remove all allergenic materials and the product will be tolerated by the allergic or sensitive individual.

The following review of the history cosmetic regulation and the current regulatory framework will help to clarify these issues listed above.

**History of the FDA mandate**

Cosmetics were unregulated in the United States 80 years ago; however, the 16 cases of blindness associated with the use of Lash Lure Eyelash aniline dye in the 1930s \(^3\) impelled Congress to take action to protect the American public. The resulting passage of the (Copeland-Lea) Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) \(^4\) set the regulatory infrastructure for cosmetics, based on the prevailing knowledge. It was modified in 1960 by the Color Additives Amendment \(^7\) and again in 1966 by the Fed. Fair Packaging and Labeling Act, \(^8\) which set forth further FDA mandates.

At the time that the Food, Drug, and Cosmetic Act was passed, not much was known about the normal physiology of the skin, and far less was known about the effect of topically applied hygienic or decorative products on the skin. Most of the study of the structure and function of skin was oriented towards disease processes. Normal skin was viewed as having an almost “Saran Wrap” like function.

Today, we know much more about the function of healthy skin, partly because of the plethora of research conducted in cosmetic industry laboratories as well as from industry support of basic science investigations in university and other institutional settings. We also now know that many cosmetics, formulated of ingredients “generally recognized as safe” (GRAS), certainly do affect the structure and function of skin and that there are many well-studied actives that offer more than just adornment or cleansing of the skin.

These factors, however, were not a consideration in 1938 when Congress defined the words, “drug” and “cosmetic” with a clear-cut distinction. According to the statutory definition, drugs are “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man... and articles intended for use as a component of any such articles.” \(^9a\) Another part of the statutory drug definition states that any substance that is intended to alter the structure or any function of the body of man (including physiologic processes thereof) is also considered to fall under the “umbrella” of “drug” \(^9b\).

Cosmetics are “articles 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 and articles intended for use as a component of any such article, except that such term shall not include soap.” \(^9c\) Thus, drugs were used to treat and prevent disease, and cosmetics were used to clean or change the appearance of the skin by adornment or ornamentation.

Congress specifically put more stringent controls on the manufacture and preparation of foods and drugs than on cosmetics because of the potential greater hazard from ingestion of substances than from the application of products used for personal grooming or beautification. Through the FDCA and its amendments, the FDA was authorized to regulate aspects of cosmetic safety, manufacture, ingredients, labeling, and advertising. An overview of the current state of affairs of regulation of cosmetics follows.

**Product safety**

Product safety is difficult to ensure because the FDCA did not mandate premarket approval of cosmetics, which is in sharp contrast to the tightly controlled marketing of drugs. Congress did not discuss how the FDA should ascertain cosmetic product safety; there are no defined measures for safety testing. The FDA requires that if the product incorporates untested ingredients or if the final product is untested, a safety warning must be placed on the products that states: “Warning—the safety of this product has not been determined.” \(^10\) The actual types of testing, and the adequacy and rigor of testing, are left to the discretion of the manufacturer. \(^11a,b\)

**Good manufacturing practice**

The FDA is empowered to prevent adulteration and misbranding of the product. To facilitate safe product manufacturing practice, because it has not been mandated to issue definitive regulations, the FDA has issued good manufacturing practice (GMP) guidelines, which are patterned after the food GMP regulations. These guidelines state that products must be prepared in a clean environment under sanitary conditions and must not contain any poisonous, filthy, putrid, decomposing, or otherwise deleterious substances in order to avoid adulteration. \(^12\)

The FDA refers to both the Bacteriologic Analytical Manual, published by the Association of Official Analytical Chemists, and the Cosmetic, Toiletry, and Fragrance Association (CTFA) guidelines for its guidance documents. Misbranding refers to misleading or incomplete information on package labeling, improper labeling of ingredients, or improper packaging. \(^13\)

**Ingredients and product composition**

According to FDA guidelines, any component ingredient may be used as long as it is “safe.” A precise review of selected ingredients is done by the Cosmetic Ingredient...
Review (CIR) Expert Panel. The CIR was established by the CTFA and the Consumer Federation of America in 1976. The panel meets frequently to assess cosmetic ingredients in an unbiased, open, and expert manner, after which the results are published. The review list is prioritized by the extent to which the public is exposed to the ingredient and its potential biologic activity. Thousands of ingredients are used in modern cosmetic manufacturing that are GRAS substances, based on industry testing many years ago and historical usage. Thus far, the CIR has only been able to definitively review hundreds of them. Ingredient safety remains an issue both in the United States and internationally.

Some companies that promote their products as “cruelty-free” or “not tested on animals” do not display the warning label that the safety of the product has not been established. They either rely on the suppliers of ingredients or contract with outside laboratories to do the animal testing. Others may use historical studies of similar products, or may use the literature, raw material safety testing, or perform clinical human safety testing to satisfy the safety requirement. Most raw materials used by these companies were tested in animals years ago, which has been recognized as the gold standard.

Unlike other ingredients, the FDA exerts strict regulatory control over coloring agents used in cosmetics as well as a small number of banned or restricted ingredients. Of all the ingredients in use, colors are the only ones that must be preapproved. All batches of petroleum-derived color additives (except for hair dyes) must be tested and certified in the FDA Color Certification Branch Laboratories before being sold. Particular colors are approved for specific end uses, for example, for coloring the final formulation vs making a colored decorative cosmetic. Of particular note is that none are approved by the FDA for tattoos.

Product labeling

Labeling laws were established to help the consumer make value and function comparisons. They were also created to enable the consumer to avoid potential allergens. Accurate labeling includes clear placement on the product label of its identity, the name and address of the manufacturer, the distributor, the quantity of the product contained therein, and the ingredients listed in rank order, using specific nomenclature, to 1%. Trade secrets and specific flavorings or fragrances are exempt from this and may be listed as “other ingredients” or may be listed in any order at concentrations of less than 1%. All safety warnings related to the use of the product must also be placed prominently on the label.

Truth in advertising

Truthful advertising is coregulated by the Federal Trade Commission (FTC) and the FDA. The FTC regulates print and electronic advertising; the FDA regulates the package labeling, which includes the product package, any insert and instructions, and the Web site, under certain circumstances, so there is considerable overlap. The FDA is mandated to prohibit “misbranding.” This means that the label must not be misleading or false, must contain the accurate product identity and all the other labeling information, and must not contain any nonapproved color additive.

FDA activities

Today, cosmetics are regulated by the FDA’s Center for Food Safety and Applied Nutrition (CFSAN). OTC drugs that may also have a cosmetic function are regulated jointly through the Center for Drug Evaluation and Research and CFSAN. CFSAN fulfills its broad responsibilities by issuing guidelines and performing field inspections, surveillance, and registration of manufacturers through the Voluntary Cosmetic Registration Program, which registers the sites of manufacture as well as the formulation and raw material composition of the products. CFSAN also keeps product experience reports, which are reported to the CFSAN Adverse Experience Reporting System. Much of its regulation of cosmetics involves postmarket enforcement because, as has been emphasized, it does not have the premarket statutory authority to approve cosmetic products, cosmetic ingredients, or cosmetic labeling.

Time is allocated each year by the field staff for routine inspections and investigations of the regulated products. The resources devoted to its enforcement efforts are somewhat limited, however, because of higher-priority obligations, including concerns about drugs, devices, biologics, food defense, and safety. Thus, the field offices are directed to inspect the cosmetic firms with the greatest potential for health hazard, such as producers of eye area products or those that have had past violations. Inspections may be triggered for other reasons, such as notification to the FDA of a complaint or adverse event from a consumer, health professional, or industry. In addition, a voluntary recall of a product, ongoing compliance situations, and follow-up to product promotion or scientific studies, may all lead to an onsite inspection by the FDA.

Violators of the adulteration and misbranding provisions of the FDA may be subject to a variety of enforcement tools, including formal correspondence such as warning letters, which may be on the FDA Web site, and publication in the press, product recalls and seizures, targeted establishment inspections, and sampling programs. If a product has been misbranded or adulterated, the FDA may request a “voluntary recall.” The product may be seized if there is a serious violation, and an injunction may be issued against further commercial operations. Rarely, criminal prosecution ensues.
Recent examples of warning letters on the FDA Web site include products that have been found to have bacterial contamination and incorrect ingredient listings. A well-known example of a seizure is case from the 1990s of Rio Hair Relaxer, imported from Brazil. It was removed from the U.S. market because its use resulted in hair loss, severe dermatitis, and hair discoloration for more than 3000 people.25,26

Another, more complex case and recent seizure is that of Age Intervention Eyelash, manufactured by Jan Marini Skin Research, San Jose, California. The product, which was promoted as a cosmetic that increased eyelash growth, contained bimatoprost, a prostaglandin analog drug that is FDA-approved to treat glaucoma. Bimatoprost has well-known side effects of darkening and lengthening lashes, the iris, and periorcular skin. Potential side effects could also include compromised vision in those already receiving the drug for medical purposes. It was seized by the FDA for the unapproved use of a drug active ingredient (ie, as an adulterated cosmetic) as well as for misbranding because it was promoted to alter the structure of a tissue in the body.27 Subsequently, a bimatoprost solution product has received FDA approval for this same purpose, but as a drug, not a cosmetic. Studies were submitted to the FDA with the rigor required for drug approval.

**Cosmetic or drug?**

Data now show that many cosmetic products, previously thought to be inert, have an effect on the structure or function of skin. The classification of a product has tremendous ramifications on its production and marketing. In general, the FDA reviews the types of product claims made to determine whether it is a cosmetic or a drug.

The FDA is guided by the intended use, which is inferred from promotional materials such as the labeling, advertisements, oral and written statements, and testimonials.28 These can be used as evidence of drug intent, even if the manufacturer issues a disclaimer. In many cases, however, no clear line of differentiation exists between cosmetic and drug claims. The cases are reviewed individually based on all of the involved facts, not on a simple phrase taken out of context, but instead on how the product in total is labeled and promoted. This is similar to Supreme Court Justice Potter Stewart’s statement regarding pornography, “I shall not today attempt further to define the kinds of material I understand to be embraced... but I know it when I see it.”29

Manufacturers have some latitude to engage in hyperbole and “creative” marketing about the benefits of the product, but they cannot engage in misrepresentation or impute physiologic or therapeutic properties to a product. If they make physiologic (eg, disease prevention) or pharmacologic claims, they must then comply with the drug or device provisions of the FDCA. Most manufacturers would like to prevent their products from being labeled “drugs.”

The primary reason companies try to avoid a drug claim is economic. There are multiple regulatory interfaces within the drug approval process and, in contrast, few hurdles in bringing a cosmetic to the market.

An example is the time and expense required to bring Renova to the market. Its active ingredient, tretinoin, was already legally marketed for decades as a treatment for acne vulgaris (as Retin-A), with a well-established safety profile. It took almost a decade and millions of dollars before the approval was granted this drug for cosmetic use in wrinkle smoothing and for treatment of tactile roughness, mottled hyperpigmentation, and correction of photodamage indications. The important distinction is that although the product was marketed for cosmetic “indications,” it was never marketed as a “cosmetic.”30

**Going to market: drug vs cosmetic**

To legally market a drug, a manufacturer must submit to the FDA a premarket application (PMA). The PMA includes defined clinical studies documenting safety and efficacy for a specific indication, with statistical significance ($P < .025$). The efficacy is determined by a specified end point (eg, microbiologic cure, cancer remission), depending on the class of drug.31 In contrast, no preapproval is necessary to market a cosmetic,32 and no predetermined end point is necessary for efficacy or product claims.

For a pharmaceutical drug, safety studies are required to generally include animal, toxicology, pharmacokinetics, pharmacology, drug-drug interaction, and other relevant data. In comparison, a cosmetic must be safe for intended use, but there is no definition of safety and there is great latitude for its documentation.

Another important aspect of marketing a product is its label. A drug has extremely complex labeling requirements, with an extensive package insert that includes a description of the chemical structure of the active ingredient, formulation, strength, additives, clinical pharmacology, mechanism of action, indications for use, contraindications, precautions, warnings, adverse reactions, dosage, and forms. The requirements for labeling of a cosmetic are well defined by regulation, but are far less complex, as previously noted.

Pharmaceutical manufacturing facilities have a mandatory registration and inspection requirement that may be repeated every 2 years. GMP regulations apply. The cosmetic facility should follow the GMP guidelines and should comply with the Voluntary Cosmetic Registration Program, but can expect infrequent surveillance.

All drug ingredients must be preapproved, including active ingredients and fillers, which are often from the GRAS list. Any change in formulation must be reviewed by the FDA. This is clearly distinct from the cosmetic ingredient regulations, where a change in formulation is a matter of course—a business decision—and not reviewed with the FDA.
The FDA closely monitors the language of drug marketing claims to ensure that approved indications are correctly promoted in advertisements and labeling. The adept drug manufacturer consults with the FDA before issuing labels and launching advertising because it understands the level of regulatory scrutiny is high and the consequences are costly. In contrast, cosmetics claims are seldom monitored and are only investigated if brought to the attention of the appropriate agency. There is no statutory mandate allowing the FDA to monitor performance advertisements and no approval process for claims.

The time and cost for drug development are in sharp contrast to those of cosmetics. The average time for drug development is from 7 to 15 years from the laboratory to the pharmacy shelf. The time for cosmetic development of a breakthrough technology is 3 to 5 years. The average cost of research and development for a new drug is $800 million. In contrast, the cost of creating and developing a breakthrough cosmetic technology is between $2 and $3 million (personal communication: Maria Corbiscello, January 22, 2007 Studio MC³). The costs, time, and effort expenditures are why the drug classification is avoided by the cosmetic industry and why it actively works to prevent the imposition of further regulation of their products.

Product claims

Product claims are the cornerstone of effective marketing in the cosmetic industry. To support their product performance claims, cosmetic companies rely on a variety of methods of substantiation:

1. Clinical evaluation is meaningful when it is blinded, controlled, and when clinical grading is done by an expert, unbiased evaluator. “Antiwrinkle,” “shiner hair,” and “smoother skin” are examples of the claims that may be made from this type of study.

2. Instrumental assessment can provide insights into the mechanism of action of the product and can objectively measure its physiologic effects. Instrumentation found in the industrial laboratory commonly includes techniques to determine trans-epidermal water loss, barrier function, surface irregularities, wrinkle depth, skin firmness, elasticity, and epidermal turnover. These tests are often performed in volunteers, but may include animal and in vitro studies. The latter are interesting but have less real-world application. A limitation of both in vivo and in vitro studies is that one cannot do a placebo control. Because even bland substances have an effect on the structure and function of skin, controls are generally obtained from the vehicle. A major limitation of both animal models and in vitro systems is the inability to accurately assess percutaneous penetration in humans. The claims obtained from these studies focus on physical properties.

3. Subjective assessment is generally a sensory evaluation. It is valuable, because the consumer may perceive changes before they are clinically evident to the observer. Types of claims from this testing include statements like “feels softer, smoother, looks more radiant” and also includes “appears to reduce the appearance of...” or “helps to heal.”

4. Product formulation claims, such as “contains X, contains 5% of aloe vera, more concentrated,” relate to the constituents of the product. Of course, the active ingredient must be stable in the final formulation, able to penetrate the corneum, and be biologically active at the target site for clinical benefits to ensue. The consumer may be unaware of the effectiveness of the ingredient in the final formulation.

5. Performance characteristics may be assessed with use tests such as the 28-day repeat insult patch test or open patch testing. These may generate claims such as “gentler,” “milder,” and “noncomedogenic.” “Unscented” is a straightforward performance claim. “Hypoallergenic” has no federal definition or standard and can mean whatever the manufacturer wants it to mean.

6. Endorsement claims include testimonials by citizens and celebrities, “tested by dermatologists,” and “developed by dermatologists.” Increasing numbers of physician named or associated brands are promoted for the marketplace. Many of these physicians are actually paid “spokesdoctors.” Products are also labeled with various institutional “seal of approval” emblems.

7. Cultural claims include “100% natural ingredients” and “no animal testing.”

8. Superiority claims include “milder than...,” “more soothing than...,” “more hydrating...” etc. The manufacturer must be prepared to substantiate the claim, under normal use conditions.

9. Emotive claims such as “Because I’m worth it (L’Oreal)” or “you’ll look like a million dollars” do not require substantiation.

10. Preference claims should be documented with a fair comparison study.

11. Mind claims are a new area relating to how the product makes one feel. Some may consider them a subclass of subjective assessment claims, but they are based on innovative assessment tools, including detailed questionnaires and instrumentation such as functional magnetic resonance imaging.

12. “Puffery” claims are those which make fanciful or outrageous claims. Puffery is a legal term that
refers to promotional statements and claims that express subjective rather than objective views, such that no reasonable person would take literally. The FTC Policy Statement on Deception states, “The commission generally will not pursue cases involving obviously exaggerated or puffing representations, i.e., those that the ordinary consumers do not take seriously.”

Nongovernmental controls also exist on product promotional claims. The National Advertising Division (NAD) of the Council of the Better Business Bureaus is a self-regulating organization that evaluates claims for truth and accuracy. If a promotional claim is found to be questionable and cannot be satisfactorily resolved by the NAD Case Report Process, it is referred to the National Advertising Review Board (NARB), and if it is not settled there, the NAD/NARB will refer it to the FTC.

Conclusions

The cosmetics industry today holds a unique position. Cosmetic companies are permitted to create and market products that are known to have an effect on the structure and function of skin, with little regulation. Most consumers purchase and cannot be satisfactorily resolved by the NAD Case Report Process, it is referred to the National Advertising Review Board (NARB), and if it is not settled there, the NAD/NARB will refer it to the FTC.39

References
