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Introduction

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Although cosmetics for the purposes of beautifying, perfuming, cleansing, or for rituals have existed since the origin of civilization, only in the twentieth century has great progress been made in the diversification of products and functions, as well as in the safety and protection of the consumer.

Before 1938, cosmetics were not regulated as drugs, and cosmetology could often be considered a way to sell dreams rather than objective efficacy. Safety for consumers was also precarious at times. Subsequently, the Food and Drug Administration (FDA), through the Federal Food, Drug and Cosmetic Act, regulated cosmetics that were required to be safe for the consumer.

With industrialization, many new ingredients from several industries (oleo- and petrochemical, food, etc.) were used in the preparation of cosmetics, often introducing new functions and forms. For better control of these ingredients, U.S. laws have required ingredient classification and product labeling since 1966.

The latest innovation in the field of cosmetics is the development of active cosmetics. Currently, cosmetics are not only intended for the improvement of the appearance or odor of the consumer, but are also intended for the benefit of their target, whether it is the skin, the hair, the mucous membrane, or the tooth. With this functional approach, products became diversified and started to claim a multitude of actions on the body. Subsequently, the cosmetic market greatly expanded, becoming accessible to millions of consumers worldwide. The competitive environment also pushed manufacturers to promise more to consumers and to develop cosmetic products of better quality and higher efficacy. Today, many cosmetic products aim at hydrating the skin, reducing or slowing the signs of aged skin, or protecting the skin against the multitude of daily aggressions that it encounters. In order for cosmetic products to support these activities, raw materials became more

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efficacious, safe, bioavailable, and innovative, while remaining affordable. With the continuous improvement of the basic sciences and the development of new sciences (e.g., molecular biology), new sources for pure raw material have been found. Raw materials are not only produced from natural sources and highly purified, but can also be specifically synthesized or even produced from genetically manipulated microorganisms. However, the availability and use of these sophisticated and active ingredients are not always sufficient for them to be optimally delivered to their targets and to sustain their activity. The cosmetic vehicle is also crucial to obtain this effect, and the role of the formulator is to combine the right ingredient with the most appropriate vehicle.

Additional sciences also developed parallel to active cosmetology and contributed significantly to its rise; this is the case for biometric techniques, which have been developing for two decades now and allow a progressive and noninvasive investigation of many skin properties. Instruments and methods are now available to objectively evaluate and measure cutaneous elasticity, topography, hydration, turn-over rate, or even to see directly in vivo inside the skin through microscope evolution. The major innovations in the field are reported by the International Society of Bioengineering and the Skin. Guidelines for the appropriate usage of instrumental techniques and for the accurate measurement of skin function and properties are regularly published by expert groups such as the Standardization Group of the European Society of Contact Dermatitis or the European Group for Efficacy Measurement of Cosmetics and Other Topical Products (EEMCO). Today, any claimed effect of a cosmetic on the skin should find appropriate techniques for a clear demonstration.

For better protection of the consumer against misleading claims, national or federal laws prohibit false advertisement on cosmetic products. More recently, the Sixth Amendment of the European Directive on Cosmetic Products has required manufacturers to have a dossier with the proof of the claims made on their products readily available.

Finally, the recent evolution of cosmetic products and the constraints imposed on the cosmetic manufacturer have led cosmetology to largely increase its credibility before scientists, physicians, and consumers. Cosmetology has become a science based on a combination of various types of expertise, whether they are in chemistry, physics, biology, bioengineering, dermatology, microbiology, toxicology, or statistics, among others.

Because of this complexity in cosmetic science, it is not possible to cover in a useful manner all the aspects of cosmetology in only one book. Details of most of the aforementioned fields are covered in different volumes of the Cosmetic Science and Technology series. With the *Handbook of Cosmetic Science and Technology*, we aim to produce a useful guide and source of innovative ideas for the formulation of modern cosmetics. The esteemed contributors to the handbook review many of the major ingredients, major technologies, and up-to-date regulations throughout the world that the formulator needs to know. For more experienced scientists, recent innovations in ingredients and cosmetic vehicle forms are described, which should orient the type of products of tomorrow. Finally, the large overview of cosmetic formulations should serve the dermatologist who is faced with patients requesting recommendations for the most appropriate product for their skin type or who have specific intolerance to an ingredient. This should help them to better understand cosmetics.

For easier access to the information contained herewith, the handbook has been subdivided into nine parts, such including several chapters written by different authors. It may seem to some an excessive number of contributors, but we intentionally chose this format to guarantee that each subject is described by recognized experts in the field who

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are well aware of the latest developments in their topic. In addition, authors were selected worldwide. Indeed, cosmetology is universal, but there exists some regional specificity that should be addressed.

The first three parts present the reader with a series of generalities going from definitions of cosmetics, to a description of the anatomy and physiology of the body targets for cosmetics, to safety terminology, and finally to a description of the principles and mechanism of unwanted interactions of cosmetics with their target.

Part 4 covers cosmetic vehicles with a special emphasis on a few types of recently introduced delivery systems, such as cosmetic patches and iontophoresis. Part 5 describes cosmetic ingredients. For some categories of ingredients, the most useful information is a list of the ingredients they comprise, with a critical analysis of the advantages and disadvantages for each. For others, however, a good understanding is needed of the role of an ingredient in a product, its limitations, its mechanism of action, and its regulatory constraints.

Part 6, the largest section, is the core of the handbook and provides guidance to the formulation of skin cleansing products, skin care products, hair products, oral care products, and decorative products. Chapters 58 and 59 cover special cosmetics for infant and elderly consumers.

The last three parts of the handbook compare the cosmetic legislation in the United States, Europe, and Japan; briefly describe how to control the stability of cosmetic products; and give an overview on the clinical tests often performed for proving efficacy, tolerance, or perception of the products. These latter chapters, however, remain quite general, being more extensively covered in other, more specialized volumes.

Given the number of contributions and the need to publish them while they are still current, it has been a formidable challenge to edit the handbook; if we have succeeded, it is attributable to the dedication of the authors and the continuous follow-up made with the authors by Sandra Beberman and Jane Roh from Marcel Dekker, Inc. We thank all of them for making this enormous task easy, enjoyable, and mainly feasible.

In view of the evolution of cosmetology over these past years, and seeing where we are today, we would like to conclude this introduction with a question that came after reading these outstanding contributions: How will cosmetology continue to evolve without reaching and overlapping the pharmaceutical field in the future? There is still a margin, but this margin is becoming increasingly thinner. Has the time arrived to describe, after the ''functional'' or ''active'' cosmetology, the cosmetology of regulators?

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Definition of Cosmetics

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INTRODUCTION

Cosmetics are a category of consumer products marketed worldwide, the purpose and functions of which are universal to people of all cultures. The 1998 global cosmetics and toiletries market was valued at $125.7 billion [1], including skincare, fragrance, haircare, personal hygiene, and makeup products. In the United States alone there are over 1400 domestic manufacturing and repacking establishments, which in the aggregate use more than 10,500 different cosmetic ingredients [2] and a corresponding number of fragrance ingredients to make over 25,000 product formulations [3]. Once considered luxuries by consumers of modest economic means, cosmetics and toiletries are seen today as necessities by growing numbers of consumers, regardless of their relative states of affluence [4]. Indeed, cosmetics are regarded not as mere pampered indulgences, but as key aids to maintaining and promoting better standards of personal hygiene and health. Yet, what are these products that we call *cosmetics*?

COSMETICS IN HISTORY

The word ''cosmetic'' is derived from the Greek *Kosm tikos*, meaning ''having the power to arrange, skilled in decorating giving *kosmein*, ''to adorn,'' and *kosmos*, ''order, harmony'' [5], but the true origin of cosmetics probably lies further still in antiquity, because early cave paintings of 30,000 years ago depict the use of body adornment (rudimentary cosmetics) in the rituals of mating and hunting [5].

Throughout the recorded history of man, cosmetics have been used with essentially the same three goals in mind, namely (1) to enhance personal appeal through decoration of the body, (2) to camouflage flaws in the integument, and (3) to alter or improve upon nature (6). Consider several historical vignettes showing the role of cosmetics down through the ages (4–6). Vases of alabaster and obsidian for cosmetics discovered by Flinders Petrie in 1914 illustrate that the ancient Egyptians were well versed in the use of eye and face paints, body oils, and ointments. Theophrastus (363–278 B.C.), a student of Aristotle, demonstrated considerable knowledge of the compounding of perfumes, and the Roman physician, Galen of Pergamon (130–200 A.D.), is said to have innovated that time-honored toiletry: cold cream (Cera Alba). Other people throughout the Middle East as

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well as the Orient were reported to have made extensive use of cosmetics. The Babylonians were said by Herodotus (490–420 B.C.) to be well practiced in the use of depilatories and the eye adornment, kohl, while Alexander the Great (356–323 B.C.) reported the use of unguents, incense, and other cosmetics by the countries of the Indo-Sumerian civilization. In Tudor England of the 1500s, sycophants of the Virgin Queen, Elizabeth I, adopted whatever cosmetic artifice and whimsy she chose to champion, whether by powdering their faces with the toxic lead paint, ceruse, to simulate the Queen's pale complexion, rouging their cheeks with red ochre, or dyeing their hair orange to simulate the Queen's once-abundant wavy red-gold hair, which she had inherited from her father, King Henry VIII. In the 17th century, the phrase ''makeup'' was first used to connote ''cosmetics'' by the poet Richard Cranshaw (1612–1649), while author and playwright Ben Johnson satirized women who ''put on their faces'' upon rising each morning before facing the world.

STATUTORY DEFINITION OF COSMETICS

Consumers possess a reasonable operational understanding of what a cosmetic does (i.e., its so-called function). The average consumer envisions a cosmetic to be a product such as lipstick, cold cream, facial foundation powder, nail polish, and other so-called decorative personal-care items of makeup, which are all designed to enhance superficial appearance and beautify the body. Frequently, the consumer will also equate the term ''cosmetic'' with ''toiletry,'' at which point other topical preparations intended to cleanse and perfume the body are also included in the layperson's operational definition of the term.

Despite the increasingly systematic and objective science associated with the art, formulation, and manufacture of cosmetics, our operational understanding of costmetics has to the present date failed to produce a corresponding harmonized international statutory agreement concerning what a cosmetic is and what the legitimate functions of such a product ought to be before it ceases to be a bonafide cosmetic. In the United States, the statutory definition of cosmetic enacted in the 1938 Federal Food, Drug, and Cosmetic Act (hereinafter, the Act) is more far reaching than the lay definition and implicitly addresses intended use as much as it does beauty-enhancing attributes of a ''cosmetic'' [7].

The term ''cosmetic'' is defined in Section 201 (i) of the 1938 Food, Drug, and Cosmetic Act (FD&C Act) as:

> . . . 1) 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 2) articles intended for use as a component of any such articles; except that such term shall not include soap . . .

The Act thus views cosmetics as articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance. No mention is explicitly made in this denotation of whether achieving such improvements in beauty, attractiveness, or appearance can legitimately be accomplished by a cosmetic product through its efficacy in affecting the body's structure or functions. The implications of such efficacy are taken into account in the treatment of the term ''drug'' by the Statute (see the following).

The 13 subdivided cosmetic product categories currently recognized by the U.S. Food & Drug Administration (FDA) for the voluntary filing of cosmetic product ingredient composition statements are enumerated in Title 21 of the Code of Federal Regulations

(c.f., 21 CFR 720.4); these are presented in Table 1. Here one can find all of the product categories that the consumer usually connotes with the terms ''cosmetics & toiletries.'' Included in the definition of cosmetics are products intended to cleanse the body in the bath or shower, mask the various malodors of the oral, perigenital, and axillary regions of the human anatomy, adorn the face, eyes, hair, and extremities in fashionable topical ''decorative'' colors, alter the color and style of the scalp hair, and afford the integument conditioning against losses of moisture caused by changes in environmental conditions (i.e., sun, wind, relative humidity) [8]. Note that the Act includes in the definition of ''cosmetic'' any material intended for use as a component of a cosmetic product, so that an ingredient intended to be used in a cosmetic is also considered to be a cosmetic.

Soap products, consisting primarily of an alkali metal salt of free fatty acids, making no label claims other than cleansing of the human body, and labeled, sold, and represented only as soap are not considered cosmetics under the law (c.f., 21 CFR 701.20). However, detergent-based ''beauty or body bars,'' so-called combination or combo-bars based on mixtures of soap and detergent(s), and those products containing other functional cosmetic ingredients (i.e., emollients, moisturizers, or botanical ingredients) that make product performance claims other than cleansing of the human body, are considered ''cosmetics.'' Additionally, soaps that contain antimicrobial active ingredients and that make antibacterial or germ-killing efficacy claims are regulated under the FD&C Act as ''over-the-counter'' (OTC) drug products. If they make cosmetic claims as well they may also be regulated as cosmetics [8] (see the following).

Other authoritative treatises in cosmetic science such as those of Jellinek [9], Poucher [5], deNavarre [10], Balsam and Sagarin [11], and *Harry's* [12] discuss cosmetic product formulations in similar categories to those that have been adopted by regulation under authority of the Act in the United States. Jackson [13] also presents an excellent and up-to-date tabulation of the product types that could reasonably be considered, wholly or in part, cosmetics. These include, as he correctly notes, some topical OTC drug products among his count of 77 product types, in addition to those products that the FDA would consider bonafide cosmetics.

The Act also contains statutory provisions to regulate cosmetics in order to ensure that only products deemed safe for their intended use and properly labeled are legally offered for sale in the United States. Thus, various prohibited actions are defined in Section 301 of the Act that relate to the conditions under which cosmetics are deemed to be ''adulterated'' (Section 601) or ''misbranded'' (Section 602) under the Act. These regulatory provisions will be discussed in Chapter 62.

COSMETICS THAT ARE ALSO DRUGS: THE INTENDED USE DOCTRINE

All topical products are not necessarily cosmetics. Dermatologics, for example, are topical products generally regulated as drug products based on the therapeutic or medicinal purpose for which the product is marketed as well as its formulation, which includes one or more pharmacologically active ingredients. Section 201 (g)(1) of the FD&C Act defines the term ''drug'' as:

> . . . (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than

TABLE 1 Cosmetic Product Categories (21 CFR 720.4)

Baby Products
Baby shampoos
Lotions, oils, powders, and creams
Other baby products
Bath Preparations
Bath capsules
Bath oils, tablets, and salts
Bubble baths
Other bath preparations
Eye makeup preparations
Eyebrow pencil
Eyeliner
Eye lotion
Eye makeup remover
Eye shadow
Mascara
Other eye makeup preparations
Fragrance Preparations
Colognes and toilet waters
Perfumes
Powders (dusting and talcum, excluding aftershave talc)
Sachets
Other fragrance preparations
Hair Preparations (Noncoloring)
Hair conditioners
Hair sprays (aerosol fixatives)
Hair straighteners
Permanent waves
Rinses (noncoloring)
Shampoos (noncoloring)
Tonics, dressings, and other hair grooming aids
Wave sets
Other hair preparations
Hair Coloring Preparations
Hair bleaches
Hair dyes and colors*
Hair lighteners with color
Hair tints
Hair rinses (coloring)
Hair shampoos (coloring)
Hair color sprays (aerosol)
Other hair coloring preparations
Makeup Preparations (Not Eye)
Blushers (all types)
Face powders
Foundations
Leg and body paints
Lipstick
Makeup bases
Makeup fixatives
Rouges
Other makeup preparations
Manicuring Preparations
Basecoats and undercoats
Cuticle softeners
Nail creams and lotions
Nail extenders
Nail polish and enamel
Nail polish and enamel removers
Other manicuring preparations
Oral Hygiene Products
Dentifrices (aerosols, liquids, pastes, and powders)
Mouthwashes and breath fresheners (liquids and sprays)
Other oral hygiene products

TABLE 1 Continued

Personal Cleanliness	
Bath soaps and detergents	Feminine hygiene deodorants
Deodorants (underarm)	Other personal cleanliness products
Douches	
Shaving Preparations	
Aftershave lotions	Shaving cream (aerosol, brushless, and lather) products
Beard softeners	Shaving soap (e.g., cakes, sticks)
Men's talcum	Other shaving preparations
Preshave lotions (all types)	
Skincare Preparations (Creams, Lotions, Powders, and Sprays)	
Body and hand (excluding shaving preparations)	Foot powders and sprays
Cleansing (cold creams, cleansing lotions, liquids, and pads)	Night
Depilatories	Paste masks (mud packs)
Face and neck (excluding shaving preparations)	Skin fresheners
Suntan Preparations	Other skincare preparations
Indoor tanning preparations	
Suntan gels, creams, and liquids	
Other suntan preparations	

* All types requiring caution statement and patch test.

> food) intended to affect the structure or any function of the body of man or other animals; and (D) articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories.

The so-called Doctrine of Intended Use of an FDA-regulated product generally will govern how it is to be regulated [14]; the maxim frequently cited here that embodies this doctrine is ''You are what you claim.'' The most recent comprehensive discussion of intended use may be found in Section II.E of the August 1996 Annex to the ''Nicotine in Cigarettes and Smokeless Tobacco Jurisdictional Determination'' document issued by FDA [15].

Prior to enactment of the 1938 Act, a 1935 Senate report foreshadowed the direction that the Congress would later take in providing that the manufacturer's intended use of the product should determine if it is to be regulated as a drug, cosmetic, or some other regulatory category [14]:

> The use to which the product is to be put will determine the category into which it will fall. If it is to be used only as a food it will come within the definition of food and none other. If it contains nutritive ingredients but is sold for drug use only, as clearly shown by the labeling and advertising, it will come within the definition of drug, but not that of food. If it is sold to be used both as a food and for the prevention or treatment of disease it would satisfy both definitions and be subject to the substantive requirements for both. The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is put . . .

Thus, the definitions of drug and cosmetic are not mutually exclusive. A product may legally be a cosmetic, a drug, or both a drug and a cosmetic. Products that are cosmetics but

are also intended to treat or prevent disease, or otherwise intended to affect the structure or any functions of the human body, are also considered drugs under the Act and must comply with both the drug and cosmetic provisions of the law [8].

Examples of products that are drugs as well as cosmetics are anticaries (fluoride) toothpastes, hormone creams, suntanning preparations containing a sunscreen active ingredient and either intended to protect against sunburn or make tanning claims [16], antiperspirants and/or deodorants, antibacterial detergent bars or soaps, and antidandruff shampoos. Most currently marketed cosmetics that are also drugs are OTC drugs. Several are new drugs for which safety and effectiveness had to be proven to FDA (i.e., in a New Drug Application or NDA) before they could be marketed [8]. A ''new drug'' is defined in Section 201 (p) of the Act as a drug that is not ''generally recognized as safe and effective'' (GRAS/E) by experts under the conditions of intended use or that has become so recognized but has not been used to a material extent or for a material time under such conditions.

It is relatively easy to market a cosmetic. Cosmetic products can be brought to market very quickly—a fact that is clearly reflected in the rapid pace with which innovations and changes occur in the cosmetic marketplace. No premarket approval (or mandatory manufacturing establishment, product, or ingredient registration) is required. No delays are thereby incurred by the marketer while waiting for FDA approval. Nor does FDA have a statutory mandate to monitor and regulate cosmetic performance advertising claims; the Agency's oversight responsibility in this area extends only to ensure that cosmetic product package labeling is not violative with respect to ''misbranding'' (i.e., that the product performance claims are not false or misleading) [8]. More about U.S. cosmetic regulations will be said in Chapter 62.

The regulatory requirements for drugs (which are beyond the scope of this chapter) are more extensive than the requirements applicable to cosmetics. For example, the Act requires that drug manufacturers register every year with the FDA and update their lists of all manufactured drugs twice annually (c.f., 21 CFR 207). Additionally, FDA drug labeling requirements and regulatory oversight of prescription drug advertising (FTC has regulatory oversight for OTC drug advertising [17,18]) are more stringent than for cosmetics. Finally, drugs must be manufactured in accordance with Current Good Manufacturing Practice (CGMP) regulations (c.f., 21 CFR 210-211) [8].

THE COSMETIC/DRUG DISTINCTION: THE ROLE OF THE INTENDED USE DOCTRINE IN FDA ASSIGNMENT OF REGULATORY CATEGORY AND TRADE CORRESPONDENCE

The regulatory category occupied by a product clearly has a great impact on the marketing of that product. Because the drug approval process required by the Act (see previous section) is rigorous, expensive, and time consuming, marketers of personal-care products would rather market their products as cosmetics than as drugs. Some topical personal-care products are formulated in a nearly identical manner, and it is the manufacturer of the topical product that frequently determines what the intended use of the product is, and whether it should be marketed as a cosmetic or as a drug by means of statements and other representations or performance claims made on product package labeling, collateral promotional literature, and advertising. In other circumstances, whether this is done intentionally for marketing reasons or is otherwise unintentional, the manufacturer's intended

use may not be easy to discern, and it is not nearly as straightforward for FDA to determine the most appropriate regulatory category for the product. How, then, is FDA to determine whether such a product is a drug or a cosmetic?

It is the interpretation of what ''intended use'' means that has helped FDA to clarify how cosmetic products are distinguished from drugs. Needless to say it has also caused uncertainty, as topical cosmetic formulations have become more sophisticated and capable of delivering enhanced performance benefits to the consumer, or, viewed from the other end of the drug–cosmetic continuum, as dermatological drug products have been formulated with ever increasing degrees of cosmetic elegance. FDA's interpretation of cosmetic versus drug status for the various products that it regulates in the years since the enactment of the 1938 Act has been guided by several sources of information.

Labeling

Intended use is determined principally, but not solely, by the claims that are made on product labeling (i.e., all labels and other written, printed, or graphic matter either on or accompanying the product). ''Puffery'' claims [19] may draw upon the stylized artful imagery and ''hope in a bottle'' that have traditionally sold cosmetics from the dawn of the cosmetic marketing era, when the formulation of cosmetics was more art than science, to the present day. ''Subjective'' and ''objective'' claims (20) are those that can and should be substantiated, usually by focus-group panel interviews; home-placement tests, follow-up questionnaires, and phone interviews; or controlled-use medically supervised clinical studies, with or without the use of accompanying bioengineering instrument assessments of various skin, hair, eye, or nail condition paramters. The Agency has even, on occasion, determined ''intended use'' of a product based, in part, on statements made on behalf of the product by manufacturer sales associates at the point of sale, or on training and guidance provided to salespersons at the cosmetic counter.

Trade Correspondence

Early FDA guidance with respect to intended use commenced soon after passage of the 1938 Act, when the Agency issued a series of informal opinions, known as Trade Correspondence (TC), that applied the statute to specific questions and situations; some of the TCs are still relied on as support for FDA regulatory policy [21]. Such TCs were the basis for decisions setting Agency policy with respect to a cosmetic's intended use. TC-10, for example, notified marketers of cosmetic claims considered by the Agency to be ''misbrandings'' in that they are ''false and misleading'' [22], while TC-229 stated that the word ''healthful'' contained in the labeling of a tooth powder would trigger the drug provisions of the Act [23]. TC-26 held that a product's mechanism of action could be the basis of a cosmetic vs. drug intended-use determination, in that a deodorant powder inhibiting the normal physiological process of perspiration would be a drug (i.e., an antiperspirant-deodorant), but the same product merely serving as a ''reodorant-deodorant'' by absorbing the perspiration or masking the malodor would probably be a cosmetic [24]. TC-42 provided further clarification of the ''affect the body'' clause of Section 201 (g) of the Act, in stating that a topical product containing emollient ingredients whose claims to efficacy were through such temporary improvements in skin condition parameters as ''softening'' (or, by extrapolation, smoothing or moisturizing) would not necessarily be considered drugs [25]. TC-61, recently revoked in light of new science [16],

served for many years as the ''line in the sand'' for distinguishing between products that referred to sunburn protection as drugs and those represented exclusively for the production of an even tan as cosmetics [26]. Other TCs have established that ordinary facial tissue for wiping purposes is not a cosmetic [27], that other appliances used as adjuncts to, or in combination with, bonafide cosmetic products, such as manicuring instruments [28], razors and razor blades [28], shaving brushes [29], toothbrushes [29], and toilet brushes [29] are not considered devices, and that cuticle removers [30] are cosmetics rather than drugs.

FDA Case Law

The most direct guidance has been provided by Agency enforcement actions involving cosmetics that were determined to be drugs. For example, case law from the 1960s established that promotional claims for the bovine serum albumin antiwrinkle products, Sudden Change (Hazel Bishop) and Line Away (Coty), taken in the overall context of product labeling, caused these products to be classified as drugs [31,32]. The court held that advertising claims for these products, which included claims such as ''[n]ot a face lift, not a treatment,'' ''[c]ontains . . . no hormones,'' ''[y]ou'll feel a tingling sensation'', ''[n]ourishes the skin,'' '[t]ightens and goes to work on wrinkles''; ''made in a pharmaceutical laboratory,'' ''packaged under biologically aseptic conditions,'' ''a face lift without surgery,'' and ''it lifts puffs under the eyes,'' among others, established the respective vendor's intent that the article had physiological and therapeutic effects. It is important to note in these cases that, aside from the claims, there was no evidence that they exerted any real effects on the structure or function of the body. In a third court case in the early 1970s, claims that the bovine serum albumin–containing products, Magic Secret (Helene Curtis), is ''pure protein'' and ''causes an astringent sensation'' alone were considered appropriate for a cosmetic [33].

1980s Regulatory Letters

The next actions taken by FDA that served to define labeling claims that may cause a product to be classified as a drug occurred in the late 1980s. In the spring of 1987, FDA sent 23 Regulatory Letters [34] to companies that were again marketing antiwrinkle and antiaging topical skincare products with aggressive marketing claims, which were deemed by the Agency to be ''daring'' [35]. These products made claims such as ''revitalizes by accelerating the rate of cellular renewal,'' ''revitalizes skin cells and promotes the skin's natural repair process,'' ''helps stimulate the natural production of structural proteins,'' ''increases the proper uptake of oxygen and blood supply to the cells,'' ''reverses facial aging,'' ''restructures the deepest epidermal layers,'' ''increases collagen production,'' and ''provides vital nourishing supplements,'' among others. All of these claims, taken in the context of individual product labeling, were sufficient in the view of the Agency to establish intended use as a drug; indeed, it would be very difficult to use these terms and *not* trigger the structure or function definition of a drug. Again, in all of the products covered in this action, there was little expectation that they actually exerted an effect on the body outside of that which normally occurs from topical application of any conventional moisturizer. The Regulatory Letters issued by the Agency served as useful precedents of the legal rationale regarding product classification, and also provided very clear guidance

to the Industry, as had been requested in a Citizen Petition [36] concerning what label claims could get a product into regulatory difficulty.

OTC Drug Monographs: Cosmetics That Contain Active Ingredients

FDA has clearly stated that determination of intended use goes beyond direct label statements. The history of use of the ingredient, its functionality in the product, and the consumer's perception all play a role in product classification. This is the case with products that contain drug active ingredients in their formulations but do not make explicitly stated claims about the drug effects of the active ingredient. Although there is no case law that addresses product classification based on presence of active ingredients alone, this issue has been addressed over the years in regulations for OTC drug products and other actions by the Agency.

FDA acknowledged in the Tentative Final Monograph for First Aid Antiseptic Drug Products, published August 16, 1991 (56 FR 33644), that antimicrobial soap products making cosmetic claims only are not subject to regulation as OTC drugs and should not be considered in a review of drug effectiveness. The Agency further established the policy that the presence of an antimicrobial ingredient does not, in and of itself, make a product a drug, provided that no drug claim (i.e., ''kills germs,'' ''antibacterial'') is made. However, the level of antimicrobial ingredient in a cosmetic product, when such ingredient is intended only as part of a cosmetic preservative system, may not exceed the concentration provided for in the OTC Monograph. The Agency also noted in this rulemaking that the ''intended use'' of a product may be inferred from labeling, promotional material, advertising, and any other relevant factor, arguing that, based on case law, a manufacturers' subjective claims of intent may be pierced to find its actual intent on the basis of objective evidence.

Analogously, the Agency acknowledged in the Final Monograph for Topical Acne Drug Products, published in August, 1991 (56 FR 41008), that the final rule covers only the drug uses of the active ingredients and does not apply to the use of the same ingredients for non–drug effects in products intended solely as cosmetics.

FDA noted in the May 12, 1993 Tentative Final Monograph for OTC Sunscreen Drug Products (58 FR 28194) that a product may contain a sunscreen ingredient and be a cosmetic if it is not intended to protect against the sun and no claims are made about the ingredient. In these cases, the term sunscreen is not used, no SPF value is given, and the sunscreen ingredient is only mentioned in the product's labeling by its cosmetic name in the ingredient list in accordance with Agency regulations at 21 CFR 701.3. However, the presence of a sunscreen active ingredient in a product *intended* to protect from sun exposure makes the product a drug. Again, FDA noted that it is not bound by the manufacturer's subjective claims, but can find actual therapeutic intent on the basis of objective evidence. Such intent may be derived from labeling, promotional material, advertising, and any other relevant source, where ''relevant source'' can even include the consumer's intent in using the product. The Agency reaffirmed these views in the May 21, 1999 Final Monograph for OTC Sunscreen Drug Products (64 FR 27666) and codified them at 21 CFR 700.35, adding only the caveat that when a cosmetic product contains a sunscreen ingredient not intended to be used for therapeutic or physiological efficacy and uses the term ''sunscreen'' or similar sun protection terminology anywhere in its labeling, the term must be qualified by describing the cosmetic benefit provided by the sunscreen ingredient,

and this statement must appear prominently and conspicuously at least once in the labeling, contiguous with the term ''sunscreen'' or other similar sun-protection terminology used in the labeling.

The Agency provided clear guidance in the February 3, 1994 Withdrawal of Advance Notice of Proposed Rulemaking for OTC Vaginal Drug Products (59 FR 5226) that the mere presence of a pharmacologically active ingredient in therapeutically active concentrations could make a product a drug, even in the absence of explicit drug claims, if the intended use would be implied because of the known or recognized drug effects of the ingredient (i.e., fluoride in a dentrifrice or zinc pyrithione in a shampoo). Thus, although explicitly stated intended use is the primary factor in determining cosmetic vs. drug product category, the type and amount of ingredient(s) present in a product must be considered in determining its regulatory status, even if that product does not make explicit drug claims.

Finally, FDA noted in a Notice of Proposed Rulemaking concerning Cosmetic Products Containing Certain Hormone Ingredients that was published on September 9, 1993 (58 FR 47611), along with a final rule on Topically Applied Hormone-Containing Drug Products for Over-the-Counter Use (58 FR 47608), that ''certain hormone-containing products not bearing drug claims could be cosmetics depending on the levels of hormones used and whether that level of use affects the structure or any function of the body . . .''. It was noted that only these hormone ingredients present at a level below that which exerts an effect on the structure or function of the body would be acceptable for use in products marketed as cosmetics. However, if the hormone ingredient was present at physiologically active levels, then the product would be classified as a drug for regulatory purposes.

The Alpha Hydroxy Acid Situation

The alpha hydroxy acids (AHAs) have been hailed as the first examples of the new cosmeceuticals since their first appearance in the marketplace several years ago [37]. Through their promotional claims, AHAs promise skincare benefits that far exceed the humectant and moisturization attributes that were once associated with AHA salts such as sodium lactate as components of the skin's so-called natural moisturizing factor (NMF) in the cosmetics of the 1970s [38]. The scientific, clinical, and patent literature show that AHAs, as used today, probably function under at least certain conditions of formulation not only as traditional cosmetic moisturizers but as epidermal exfoliants and modulators of epidermal and dermal structure and function [39–42]. They are promoted in mass-marketed and salon-treatment products alike for treatment of a number of cosmetic (i.e., severe dry skin, tone/texture) and more significant dermatological (i.e., acneiform, photoaging, age spots) conditions [43, 44]. Manufacturers of these products have sought to market them directly to consumers as cosmetics or through phsician offices, salons, and professional estheticians [37, 45–47]. Although most marketers have artfully avoided making direct and impactful efficacy claims that might invite triggering the drug provisions of the Act [48], FDA is also cognizant that the addition of chemical exfoliants to cosmetics on such a wide scale is unprecedented [43], and 7 years of marketing history with such products may prove an inadequate and unreliable predictor of future adverse impacts on public health. Therefore, despite prior evaluations of AHA safety by the Cosmetic Ingredient Review (CIR) [49] and some more recent evaluations conducted by FDA [50] as well, the Agency has reserved its judgement concerning the appropriate regulatory category designation(s) for AHA skincare products and remains vigilant concerning the adequacy of the safety sub-

stantiation for AHAs, particularly with respect to potential chronic effects of AHAs on the sun sensitivity and photocarcinogenic responses of the skin [51].

SUMMARY: COSMECEUTICALS, COSMETIC THERAPEUTICS, AND OTHER PROPOSED DEFINITIONS

Topical products marketed in the United States are regulated under the Act, variously, as cosmetics, drugs, or OTC drug-cosmetics. There is no intermediate category that corresponds, for example, to the ''quasi-drugs,'' defined under the Japanese Pharmaceutical Affairs Law [52]. Neither are there any provisions under the U.S. statute that would accomodate classes of topical skincare products with levels of efficacy that exceed those of traditional cosmetics but whose safety have not been as rigorously substantiated as traditional drugs. Reed [53] and Kligman [54] proposed that such high performance cosmetics be classified as ''cosmeceuticals,'' despite the lack of legal standing of such a product category. Piacquadio [55] favors the term ''cosmetic therapeutics'' when referring to drugs and devices having known risk/benefit profiles and established efficacy for a cosmetic indication, pending or with FDA approval. Privat [56] suggested the categories ''decorative and/or protective cosmetics'' for those products that embellish by modifying (appearance, color, feel) or protecting the integument from external insults (i.e., UVR or bacteria), while reserving the term ''remedial and/or active cosmetics'' for those products that modify or correct the physiological state of the integument [e.g., stratum corneum (SC), epidermis, melanocytes, intercellular lipid layer, sudoral glands, hypodermis]. Morganti [57] coined the term ''cosmetognosy'' to denote the science that deals with the biological effects of cosmetics. Although these proposals each have varying degrees of merit, they, too have no regulatory standing in the United States under provisions of the 1938 FD&C Act.

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REFERENCES

1. Bucalo AJ. 1999 State of the Industry. Global Cosmet Ind, 1999; June: 32.
2. Wenninger JA, R. Canterbery R, McEwen GA Jr, eds. *CTFA International Cosmetic Ingredient Dictionary*. 8th ed., 1999.
3. FDA Compliance Program Guidance Manual 7329.001, pt. 1 at 1. August 1993.
4. McDonaugh EG. *Truth About Cosmetics*. Drug Markets, Inc. 1937: vii.
5. Butler H. Historical Background. In: Butler H, ed. *Poucher's Perfumes, Cosmetics and Soaps*, 9th ed. London: Chapman & Hall, 1993: 639–692.
6. Romm S. *The Changing Face of Beauty*. St. Louis: Mosby-Yearbook, Inc., 1992.

7. Yingling GL, Onel S. Cosmetic regulation revisited. In: Brady RP, Cooper RM, Silverman RS, eds. *Fundamentals of Law and Regulation*. Vol. 1. Washington, DC: FDLI, 1997: 321.
8. *FDA's Cosmetics Handbook*. Washington, D.C.: U.S. Government Printing Office, 1993: 1–3.
9. Jellinek JS. *Formulation and Function of Cosmetics*. New York: Wiley-Interscience, 1970.
10. deNavarre MG. *The Chemistry and Manufacture of Cosmetics*. 2nd ed. Vols. I–IV. Princeton: D. Van Nostrand Company, Inc., 1969.
11. Balsam MS, Sagarin E. *Cosmetics: Science and Technology*. Vols 1–3. New York: John Wiley and Sons, Inc., 1972.
12. Wilkinson JB, Moore RJ. *Harry's Cosmeticology. 7th ed*. New York: Chemical Publishing Co., Inc., 1982.
13. Jackson EM. Consumer products: cosmetics and topical over-the-counter drug products. In: Chengelis CP, Holson JF, Gad SC, eds. *Regulatory Toxicology*. New York: Raven Press, 1995: 105–121.
14. Yingling GL, Swit MA. Cosmetic regulations. In: Cooper RM. *Food and Drug Law*. Washington, D.C.: FDLI, 1991: 362.
15. The 'Intended Use' of a product is not determined only on the basis of promotional claims. In: *Nicotine in Cigarettes and Smokeless Tobacco is a Drug and These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act: Jurisdictional Determination*. U.S. Food & Drug Administration, Department of Health and Human Services, August 1996, Annex, Section II.E.
16. Final Rule for Over-the-Counter (OTC) Sunscreen Products for Human Use. 64 FR 27666 @ 27668. May 21, 1999.
17. Hobbs CO. The FDA and the Federal Trade Commission. In: Cooper RM. *Food and Drug Law*. Washington, D.C.: FDLI, 1991: 429–430, 452–456.
18. Memorandum of Understanding Between FTC and FDA. 36 FR 18539. 1971.
19. (a) McNamara SH. FDA Regulation of Cosmeceuticals. Cosmet Toilet 1997; *112*(3): 41–45. (b) FTC Deception Policy Statement. Letter to the Honorable John D. Dingell, Chairman, Committee on Energy and Commerce, U.S. House of Representatives, @ n42. October 14, 1983. (c) Feldman JP. Puffery in Advertising. Arent Fox Advertising Law (*http://www.arentfox.com*), June 1995. (d) Hobbs CO. Advertising for foods, veterinary products, and cosmetics. In: Brady RP, Cooper RM, Silverman RS, eds. Fundamentals of Law and Regulation. Vol. 7. Washington, D.C., 1997: 350. (e) Legal aspects of promotion strategy: advertising. In: Stern LW, Eovaldi TL. *Legal Aspects of Marketing Strategy: Antitrust and Consumer Protection Issues*. Englewood Cliffs: Prentice-Hall, Inc., 1984: 375–377.
20. (a) McNamara SH. Performance claims for skin care cosmetics. *Drug Cosmet Ind* 1985; October: 34. (b) Weinstein S, Weinstein C, Drozdenko R. A current and comprehensive skin-evaluation program. *Cosmet Technol*, 1982; April: 36. (c) Grove GL. Noninvasive methods for assessing moisturizers. In: Waggoner WC, ed. *Clinical Safety and Efficacy Testing of Cosmetics*. New York: Marcel Dekker, 1990: 121–148. (d) Smithies RH. Substantiating performance claims. *Cosmet Toilet* 1984; *99*(3): 79–81, 84.
21. Kleinfeld VA, Dunn CW. Trade correspondence. In: *Federal Food, Drug, and Cosmetic Act. Judicial and Administrative Record (1938–1949)*. New York: Commerce Clearing House, Inc., 1949: 561.
22. TC-10, (in Ref. 21) August 2, 1939: 566.
23. TC-229, (in Ref. 21) April 11, 1940: 659.
24. TC-26, (in Ref. 21) February 9, 1940: 581.
25. TC-42, (in Ref. 21) February 12, 1940: 586.
26. TC-61, (in Ref. 21) February 15, 1940: 593.
27. TC-39, (in Ref. 21) February 9, 1940: 585.
28. TC-112, (in Ref. 21) February 29, 1940: 613.
29. TC-109, (in Ref. 21) February 29, 1940: 612.

30. TC-245, (in Ref. 21) April 25, 1940: 665.
31. *United States v. An Article . . . Line Away*, 284 F. Supp. 107 (D. Del. 1968); affirmed, 415 F. 2d 369 (3d Cir. 1969).
32. *United States v. An Article . . . Sudden Change*, 288 F. Supp. 29 (E.D.N.Y. 1968); reviewed 409 F.2d 734 (2d Cir. 1969).
33. *United States v. An Article . . . Magic Secret*, 331 F. Supp. 912 (D. MD 1971).
34. FDA Regulatory Letters No. 87-HFN 312-08 to 87-HFN 312-29 (April 17, 1987 to June 23, 1987).
35. McNamara SH. Performance claims for skin care cosmetics or how far may you go in claiming to provide eternal youthfulness. Food Drug Law J 1986; *41*:151–159.
36. Citizen petition of McCutcheon, Doyle, Brown & Emerson. Bio Advance, FDA Docket No. 87P-0006, (January 6, 1987).
37. (a) Godfrey-June J. The AHA phenomenon. Longevity 1993; Sept.: 36–39. (b) Jackson EM. AHA-type products proliferate in 1993. Cosmet Dermatol 1993; *6*(12):22, 24–26. (c) Kintish L. AHAs: today's fountain of youth? Soap/Cosmetics/Chemical Specialties 1994; Feb: 26–31.
38. (a) Harding CR, Bartolone J, Rawlings AV. Effects of Natural Moisturizing Factor and Lactic Acid Isomers on Skin Function. In: Loden M, Maibach HI, eds. *Dry Skin and Moisturizers: Chemistry and Function*. Boca Raton: CRC Press, 2000:229–241. (b) Middleton JD, Sodium Lactate as a Moisturizer. *Cosmet Toilet* 1978; *93*:85–86.
39. (a) Leyden JJ, Lavker RM, Grove G, Kaidbey K. Alpha hydroxy acids are more than moisturizers. J Geriatr Dermatol 1995 *3* (suppl. A): 33A–37A. (b) Van Scott EJ, Yu RJ. Actions of alpha hydroxy acids on skin compartments. J Geriatr Dermatol 1995; 3(suppl A): 19A–25A.
40. Smith WP. Hydroxy acids and skin aging. Soap/Cosmetics/Chemical Specialties 1993; *93*(9): 54, 56, 57–58, 76.
41. Smith WP. Hydroxy acids and skin aging. Cosmet Toilet 1994; *109*: 41–48.
42. Smith WP. Epidermal and dermal effects of topical lactic acid. 1996; J Am Acad Dermatol 35: 388–391.
43. Kurtzweil P. Alpha hydroxy acids for skin care. FDA Consumer 1998; March-April: 30–35.
44. Anonymous. Alpha hydroxy acids in cosmetics. FDA Backgrounder, BG 97-4, February 19, 1997.
45. Brody HJ. *Chemical Peeling and Resurfacing* (2nd ed.), St. Louis: Mosby-Year Book, Inc., 1997:90–100.
46. Draelos ZD. New Developments in Cosmetics and Skin Care Products. In: *Advances in Dermatology*. Vol. 12. St. Louis: Mosby-Year Book, Inc., 1997; 3–17.
47. (a) AHA '95 Preview: New Developments in Alpha Hydroxy Acids. Symposium and Live Patient Workshop, Jointly Sponsored by Cosmetic Peel Workshop and Medical Education Resources, Inc., Orlando, FL, December 3–4, 1994. (b) AHA '96 Preview: New Advances in AHAs and Skin Rejuvenation Techniques. Symposium and Live Patient Workshop, Jointly Sponsored by Medical Education Resources, Inc. and Herald Education & Research Foundation, San Diego, CA, December 2–3, 1995.
48. Yingling GL and Onel S. Cosmetic Regulation Revisited. In: RP Brady, RM Cooper, RS Silverman, eds, *Fundamentals of Law and Regulation*, Vol. 1, FDLI (Washington, DC), 1997: 341–342.
49. (a) Cosmetic Ingredient Review. Final Report: Safety Assessment of Glycolic Acid; Ammonium, Calcium, Potassium and Sodium Glycolate; Methyl, Ethyl, Propyl, and Butyl Glycolate; Lactic Acid; Ammonium, Calcium, Potassium, Sodium, and TEA-Lactate; Methyl, Ethyl, Propyl, and Butyl Lactate; and Lauryl, Myristyl, and Cetyl Lactate. Washington, D.C.: Cosmetic Ingredient Review, 1997. (b) Jackson, EM. CIR Expert Panel Releases AHA Report. Cosmet Dermatol 1997; *10*(7):37–39
50. Effects of Alpha Hydroxy Acids on Skin. Report Submitted by KRA Corporation (Silver Spring, MD) to the Office of Cosmetics and Colors, CFSAN, FDA, DHHS under Contract No. 223-94-2276. February 22, 1996.

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51. (a) Kaidbey K. An Investigation of the Effects of Topical Treatment with an Alpha-Hydroxy Acid (AHA) on the Sensitivity of Human Skin to UV-Induced Damage (FDA Sponsored Study # 1). Philadelphia: Ivy Laboratories (KGL, Inc.), 1999. (b) Kaidbey K. An Investigation of the Effects of Topical Treatment with Alpha-Hydroxy Acid (AHA) on UVB-Induced Pyrimidine Dimers in Human Skin (FDA Sponsored Study #2). Philadelphia: Ivy Laboratories (KGL, Inc.), 1999.
52. Santucci LG, Rempe JM. Legislation and Safety Regulations for Cosmetics in the United States, Europe, and Japan'', Ref. 3, *op. cit*., Chapter 20; 556–571.
53. Reed RE. The definition of 'cosmeceutical.' J Soc Cosmet Chemists 1962; *13*:103–106.
54. (a) Skin: the hot topics. Vogue 1988; October:417. (b) HAPPI, 1996; May:61. (c) Kligman AM. Why Cosmeceuticals? Cosmet Toilet 1993; *108*(8):37–38. (d) Waleski M. Reed coined 'cosmecutical.' Letter to the Editor. HAPPI 1996; August: 12.
55. Piacquadio D. Cosmetic therapeutic *vs*. cosmeceutical: which is it and why? AHA '95 Preview: New Developments in Alpha Hydroxy Acids. Symposium and Live Patient Workshop, Jointly Sponsored by Cosmetic Peel Workshop and Medical Education Resources, Inc., Orlando, FL, Dec. 3–4, 1994.
56. Privat Y. A new definition of cosmetology. In: Baran R, Maibach HI, eds. *Cosmetic Dermatology*. London: Martin Dunitz, Ltd., 1994: xiv–xv.
57. Morganti P-F. The cosmetic patch. A new frontier in cosmetic dermatology. Soap/Cosmetics/Chemical Specialties 1996; *96*(2):48–50.

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