75 General Concepts of Ethics in Human Testing

Klaus E. Andersen
Department of Dermatology, Odense University Hospital, University of Southern Denmark, Odense, Denmark

COSMETICS MUST BE SAFE

According to the European Union (EU) Cosmetics Directive (Council Directive 93/35/EEC, article 2), cosmetic products must not cause damage to human health when used under normal and foreseeable conditions of use. This is in line with the expectations in society and among consumers. Cosmetic products must be safe.

Side Effects Do Occur

However, on the other hand, consumers also know that they may experience adverse reactions related to the use of cosmetic products. Usually, the reactions are so mild that the consumers do not seek medical advice, but just stop using the suspected product or change to alternative products. A 20-year old questionnaire survey, including about 1000 individuals from the normal population in United Kingdom, showed that 8.3% claimed to have experienced adverse reactions from the use of cosmetics (1). About 1% of the study group were later shown to have allergic patch test reactions to a cosmetic ingredient. A Danish study evaluated sensitization to cosmetic ingredients in an unselected population, comprising 567 subjects patch tested with ready-to-use patch test kits (TRUE test panel 1 and 2). It was found that 3.2% of males and 4.2% of females were sensitized to cosmetic allergens in this series of 24 common contact allergens (2). From dermatological clinics also it is well documented in eczema patients that cosmetic products are a common source of irritant- and allergic-contact dermatitis. Further, there are other types of skin side effects reported; such as photosensitivity, acnegenicity, contact urticaria, changes in pigmentation, and subjective symptoms as burning and stinging sensations in the skin.

Debate on Cosmetic Safety and Ethics of Testing is Needed

This is the background for the discussion on ethics and safety issues in relation to cosmetic testing. If we do not face the ethical problems, the impression may be that they do not exist! The key notions of the scientific community are therefore an open debate among peers, enforcement of law and regulations, training of authorities, industry and safety assessors, and information to the public and debate.

TESTING OF COSMETIC PRODUCTS IS NOT COMPULSORY, BUT MAY BE WARRANTED

The EU Council Directive 93/35/EEC regulates the manufacture and marketing of cosmetic products in the EU. In theory, cosmetic ingredients and products testing can be performed in vitro, in vivo in animals, and in humans.

Safety Tests

Testing of products is not required, because in general the toxicity profile of a cosmetic product can be derived from the knowledge of the toxicity of cosmetic ingredients. The directive contains positive and negative lists of cosmetic ingredients. Most ingredients are tested according to the methods required for industrial chemicals as given by the EU or OECD, and certain types of ingredients as preservatives, UV filters, and colorants need approval prior to their inclusion in cosmetic formulations. However, industry wants additional information on the finished products under certain circumstances; for example, to test for compound effects caused by interaction between ingredients, which may change the toxicological profile of the product.

Tests to Support Claims

On the other hand product testing may also be warranted by industry to document claimed efficacy and to support marketing and not just to provide assurance about the safety of the product.

No "Cookery Book" Testing

There is no "cookery book" description on how to test cosmetic products. In predictive testing, in general, it is important to recognize that a test method only gives answers related to the type of side effect it is developed for!

Possible adverse reactions include skin irritation, contact allergy, photo-mediated reactions, acne, contact urticaria, pigment changes, hair and nail changes, subjective symptoms, and various end points measured by noninvasive techniques (elasticity, skin thickness, wringling, roughness etc.). Therefore, it is not possible to make a complete list of current testing methods. The design of the test protocol depends on the specific question asked. In each case the reasoning and the scientific background of the test should be given.

Animal Tests

For more than 50 years, animal assays for skin irritation and skin sensitization have been routinely used with success (3). They have proven good predictivity for significant skin sensitizers and corrosive and moderately irritant substances. However, the animal assays have limited discriminative power, when it comes to mild effects, as the ones expected from cosmetic ingredients and products (4). When it concerns skin irritation, the animal skin with important structural and physiologic differences compared with human skin simply lacks the multitude of reaction patterns possible in human skin. Until recent years, laboratory animal-test methods have been used for testing of cosmetic ingredients and products in spite of the inherent difficulties related to extrapolation, from animal-test data to human–consumer exposure risk. However, the 7th amendment to the Cosmetics Directive [2003/15/EC] says that safety of cosmetic ingredients and products in the future must be assured without the use of animal tests. The consumer council in Brussels has managed to reach a qualified majority agreement on the proposal to ban:

- The placing on the market after 2013 of cosmetic products, of which the final formulation is tested on animals, as well as cosmetic products containing ingredients tested on animals for those cases where validated alternative test methods are available.
- Testing final products on animals.
- Testing of ingredients or combinations of ingredients on animals, when such tests can be replaced by one or many alternative methods figuring in Annex V of Directive 67/548/EEC or in Annex IX of the cosmetics directive.

Until 2007, Annex IX of the cosmetics directive contains no alternative methods that offer consumers a degree of protection similar to the animal tests that they aim to replace. The validation process for alternative methods is complicated and time consuming, so the definitive ban is postponed until further notice. New in vivo animal data for cosmetic ingredients and formulations will not be generated. The agreement tries to strike a balance between human health and animal welfare, while abiding by World Trade Organization rules. This change could result in animal testing moving into third countries instead of avoiding them. This is because cosmetic products tested on animals outside the EU could be sold in the EU without any restrictions. As a consequence, this measure could take the pressure from the authorities and the industry to further develop and adopt alternative methods.

HUMAN SAFETY TESTS

Ethical Considerations

The risk to a volunteer participating in cosmetic testing cannot be weighed against a benefit, as is the case when testing of pharmaceuticals. Finished cosmetic products must be shown to be essentially safe prior to human exposure. Transient effects may be ethically acceptable, such as

slight irritation, whereas adverse and permanent health effects, such as sensitization or scarring, are not. A *minimal risk* is acceptable (5). This is equivalent to daily life situations where there is either a chance of a trivial reaction, such as slight eczema or sunburn, or where there is a minimal risk of a serious disability or death, comparable with that of being a passenger in a scheduled airline flight. The Food and Drug Administration has also defined minimal risk, as the probability and magnitude of harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

On the other hand, it is not sufficient to satisfy requirement for minimal risk, recruitment, and informed consent of volunteers. Clinical studies should aim to answer an experimental question that cannot be answered in any other way. The test results should add value to the understanding of the product toxicity and benefit the consumers in terms of additional safety. Studies with ill-defined aims and poor experimental design will be of no value to the product risk assessment and may just generate a false feel-good factor, and the results may be used as an unethical basis for marketing purposes. There is a gray zone to efficacy testing that can only be performed when there is evidence that the product does not cause local or systemic adverse reactions. Market research trials may give additional confidence in the degree of tolerance in the consumer population. Any adverse reaction data from such human volunteer market research trials may be useful in the evaluation of product compatibility, but this should not be the primary purpose of the trial design. The rationale for human volunteer use in cosmetics testing must be continually challenged to ensure good clinical practice and ethical justification.

Notes of Guidance

In the "Notes of Guidance for Testing of Cosmetic Ingredients for their Safety Evaluation" (6), published by the Scientific Committee on Consumer Products (SCCP), human data are mentioned as a possibility when evaluating the safety of cosmetics. However, the document does not specify these in detail. Regarding skin irritation, the SCCP considers that at present human testing of cosmetic ingredients should not be preferred to animal testing.

In this context, the scientific and ethical considerations for testing cosmetic ingredients on human subjects need to be defined more clearly. The skin irritancy reaction in humans is not an absolute measure and must be related to appropriate controls defining the range of response.

Prerequisites for Human Testing

At the European Community level, there is virtually no formal legislation addressing human experimentation.

A number of points shall be considered in relation to human tests (7):

1. Tests in animals or validated alternative methods are of limited value regarding their predictive value for exposure of a human population. Therefore, confirmatory safety tests in humans may be necessary scientifically and ethically provided that the toxicological profile of a compound is available on the basis of animal or alternative methods.
2. Confirmatory testing of compounds in humans must only be undertaken when there is adequate information to suggest that a high degree of safety is to be expected.
3. Confirmatory tests of ingredients/products in humans must be limited to situations where no irreversible damaging effects are to be expected for the volunteers, and where the study goal is reasonably achievable with a study population of limited size.
4. Human volunteers should not be employed in investigation for eye irritation and sensitization or other toxicological trials where the outcome may be irreversible.
5. The recruitment of human volunteers should be in line with the "World Medical Association Declaration of Helsinki" in its current revision: Human testing is to be conducted and monitored under the direction of relevantly trained personnel to ensure the health and well being of volunteer subjects involved in the testing. The health and welfare of the subject has first priority and is highly protected.
6. "*The Good Clinical Practice for trials on Medicinal Products in the European Community*" is a valuable guide.
7. National regulations regarding human studies should be followed.
8. Test protocols should be submitted to the responsible ethical committee.

Procedure of Irritancy Assessment in Human Volunteers

On the basis of a low irritation potential as proven by animal or future validated in vitro methods, the skin tolerability of a substance can be confirmed by testing in human volunteers. A number of test protocols are available, such as open- and closed-patch tests, single- and repeated-exposure tests, and use tests. They should be chosen on the basis of the relevant use pattern of the ingredient (8).

- In the open test, the substance is applied on the skin without occlusion for time periods between 15 minutes and 24 hours. This test allows the assessment of concentrated products.
- In closed-patch tests, diluted or undiluted products are applied under occlusive chambers over 24 or 48 hours. The test allows the comparative study of substances in the same individual.
- Cumulative or repetitive closed-patch tests involve applications on the same test site between one and seven times per week over a period of one to five weeks. These repetitive tests allow the assessment of cumulative irritation that is missed by single application tests.
- Used or repeated open application tests (ROAT) imply the repeated application of a substance closely modeled to the use situation.

While these tests historically have been assessed by clinical methods, noninvasive bioengineering technology such as measurement of transepidermal water loss or of blood flow may provide higher sensitivity and objectivity to these tests, and thereby reduce the exposure and risk to volunteers.

However, neither the above confirmatory tests nor the use of bioengineering methods have been validated according to modern scientific criteria (9).

Assessment of Sensitization Potential in Human Volunteers is Discouraged

Sensitization potential has also been investigated using human volunteers, and the development of animal sensitization tests has been partly based on comparison with human tests performed with the same chemicals (10). Further, human testing has the advantage that extrapolation of the test results from one species to another is avoided.

Human predictive skin sensitization tests have been in use for the past 50 years. They have been used more widely in the United States than in Europe. Contract laboratories have performed the vast majority of human sensitization tests, and the scientific literature contains a limited number of publications giving results from tests with cosmetic ingredients as preservatives and fragrance chemicals. There are a number of different human sensitization tests available. They vary with regard to the number of induction patch tests, the placing of the patches, and the use of a maximization step. However, it is not entirely clear how useful these variations are because validation of the tests has not kept pace with development of new tests. The human sensitization tests require great experience in design and execution of the test, and a number of artifacts are possible.

Three different approaches, for predictive testing in man, have been in use:

1. A single induction/single challenge patch test
2. Human Repeated Insult Patch Tests (HRIPT)
3. Human Maximization Test

The performance of the different test methods depends on a number of factors, including type of test substance (ingredient or finished product), chemistry and animal toxicological data available, and intended use of the product.

Concerns Regarding the Use of Human Volunteers for Predictive Allergenicity Tests

Cosmetic ingredients identified as sensitizers in animal assays or other validated assays, when existing, should not be studied in humans. The human sensitization tests are time consuming and very expensive because a large number of volunteers (150–200) are required in each test; however, considerably less number of volunteers (25) are required for the human

maximization test, which, as the name says, maximizes the response to a certain degree. The argument for reducing the number of volunteers in the human maximization test is the amplifying step introduced by treatment with an irritant test product or sodium lauryl sulfate. Further, the selection of human volunteers usually results in the use of an inhomogeneous test group (compared with the more homogeneous group used for animal experiments). The large numbers of participants in most of these tests are necessary to reduce the 95% confidence interval for the test result, otherwise the likelihood of unpredicted responses in the consumers increase. If, for instance, no positive reaction occurred in 100 induced test subjects, then for statistical reasons up to 36 of 1000 consumers may react.

In any case, it is scientifically inadequate and unethical to perform predictive tests with a number of subjects insufficient to produce valid data.

The performance of human sensitization tests raises ethical considerations, in particular concerning the risk for the volunteers, especially the risk that a patch test sensitization elicits a clinical disease in the subject.

In the literature, there is no answer on the consequences of such testing on human volunteers. A request of information about the risk involved was sent to COLIPA in December 1998. The answer dated March 22, 1999 gave the following information provided by member companies:

- Dermatological testing to confirm skin compatibility is common practice; data on 470,000 human volunteers covering 2000 products did not reveal any positive results identified as due to sensitization.
- Reported data covering HRIPT tests carried out during the last 10 years and related to 2044 different products tested on a total of 136,765 persons showed 123 cases of probable/confirmed sensitizations.

In conclusion, a risk for human volunteers cannot be excluded. There is still a lack of information on the severity and frequency of adverse effects.

Minimal Requirements for Human Testing for Other Purposes

One or more clear hypotheses should be stated in the study protocol. As a result of the study, these hypotheses will be refuted or accepted. Only a clear a priori statement of hypotheses will allow the choice of an appropriate study design, an appropriate study sample, and choice of the appropriate statistical methods.

Study Design

The design of skin compatibility studies depends on the study problem investigated. Many study designs have been described and successfully used in the past, even though there are no protocols standardized and validated according to strict criteria. The study design will depend on

- kind of cosmetic ingredient or mixture of ingredients tested;
- anticipated use of the ingredient or mixture of ingredients in cosmetic finished products; and
- kind of skin compatibility problem to be assessed (e.g., immediate or delayed effects, acute or cumulative effect).

All valid study designs for compatibility studies have to include negative and positive controls and the vehicle (blank). The scientific criteria for the choice of the study design should be clearly stated in the protocol.

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76 Values and Limitations of Bioengineering Measurements

Peter Clarys and André O. Barel

Faculteit Lichamelijke Opvoeding en Kinesitherapie, Vrije Universiteit Brussel, Brussels, Belgium

In the dermato-cosmetic world, evaluation of the skin looks at first glance rather easy since the skin is very accessible for clinical evaluation (1,2). Visual examination reveals color, dryness, oiliness, roughness, ageing, etc. Tactile evaluation by feeling reveals also dryness and oiliness, plus roughness, firmness, laxity, ageing, etc. Even olfactory examination can be carried out, which reveals information on perspiration, microbial colonization, and antiperspiration. As an example, human vision is a very sensitive sensory and neurophysiological process. Experience shows that we have a high sensitivity and discriminative power at low intensities of luminosity. Our color discriminative power is so high that 0.5% to 1% differences in color can be easily detected. Our sensitivity at higher intensity of luminosity is much less present. On the other side, this neurophysiological process is very limited, subjective, mostly qualitative, highly observer dependent, and there is no precise memorization of color in function of time. The sensitivity in the visible region is not constant in function of wavelength with a maximum of sensitivity in the green color (490–550 nm). On the contrary, the use of tristumulus reflectance colorimeters using the CIELAB L*a*b* color system, which is internationally accepted, delivers a quantitative, accurate, and reproducible analysis of the skin color and can be calibrated with standard color charts (3).

Morphological and histological informations about the different layers of the skin can be obtained by the very invasive conventional biopsies that provide information of the full skin layers down to the hypodermis (4). Skin biopsies could be envisaged in dermatology but for ethical reasons are not acceptable in the cosmetic domain.

The development of novel, ingenious, noninvasive bioengineering measuring and imaging devices as tools in the evaluation of the skin has known an enormous development within these last years. They are used in clinical and fundamental dermato-cosmetic research. The aim of bioengineering measurement strategies is also to fullfil the legal requirements concerning safety and validation of claims, mainly with the ban of animal testing on finished cosmetic products. Directive 93/35/EEC requires that evidence is provided to support efficacy claims for marketed cosmetic products (5). Although the Directive does not specify how this kind of information should be obtained, more and more efficacy claims are supported with bioengineering measurements.

The advantage of bioengineering and imaging techniques is that almost all the aspects and properties of the living skin and also the changes of the skin in health (ageing) or in pathology (e.g., psoriasis) are now measurable and quantifiable based on objective techniques, and this is done in a noninvasive way, with no pain or inconvenience caused to the subjects (1). The noninvasive methods are by nature objective, quantitative, generally investigator independent, and they can be calibrated and validated in vivo and/or in vitro on skin model systems.

About 20 years ago, Lévêque (one of the founders of the noninvasive bioengineering) was already impressed by the availability of noninvasive devices (an estimation of about 20 different devices in 1989). Currently the number is probably far above 100 to 150. The second edition of the *Handbook of Non-Invasive methods and the Skin* edited by Serup, Jemec, and Grove was published in 2006 and counts more than 100 chapters devoted to bioengineering measurements and methods (6).

Many of these instruments or techniques are nowadays commercially available (not always at affordable cost) and adapted for routine measurements. However, some of the recent devices are still experimental, developed by skillful engineers in research laboratories, and sometimes requiring experienced scientific operators.

The aim of this chapter is to critically investigate not only the principle of bioengineering methods and the advantages of testing with a bioengineering instrument but also their

limitations in applications. Problems concerning the standardization and validation will be evoked using some specific examples such as in relation with hydration and mechanical properties of the skin.

ADVANTAGES IN USING BIOENGINEERING INSTRUMENTS

The noninvasive methods are by nature objective, quantitative, generally investigator independent, can be calibrated and validated, and they are also developed to work on human volunteers. If bioengineering measurements are properly performed, under standardized conditions, then they can lead to a harmonization of the obtained results and allow interlaboratory and interobserver comparisons (7). Another important advantage of bioengineering measurements is that some of them are able to detect subclinical effects not present visually. For example, the detection of an abnormally high level of transepidermal water loss (TEWL) that can be correlated with the appearance of skin irritation at a later stage (8,9).

STANDARDIZATION, CALIBRATION, AND VALIDATION OF THE INSTRUMENTS

Each bioengineering instrument delivers raw data, which become only valid through a process of validation involving calibration and comparison with other methods or with a reference method (2). This procedure of standardization, and calibration to validate the technique and the performances, is necessary before starting a dermato-cosmetic study. Serup (2) has defined and described some classical key terms regarding the performances and validation of any instrument: accuracy, precision, range, repeatability, reproducibility, sensitivity, etc. Each commercial instrument is in principle calibrated at the factory before reaching the customer. Furthermore, the recalibration of the instrument should be performed at regular intervals (ideally, if possible, before each set of measurements). It is strongly advised that a laboratory should use the instruments according to precisely described standard operating procedures (SOPs), which cover the calibration, validation, maintenance, performance, and condition of the equipment used with all the details of the operation procedure (10).

Most of the measurements on the skin are strongly influenced by variations in the environmental conditions. Therefore the temperature and the relative humidity in the experimental measuring room should be standardized and kept constant (11). The ambient air temperature should be kept between 19°C and 21°C and the relative humidity at 40% to 45%. The subjects should be acclimatized and conditioned in the standardized environmental conditions for at least 20 minutes. The skin test sites should not be covered with any clothes and exposed to the ambient air during this 20-minute period. The influence of seasonal variations (winter and summer periods) needs to be taken into account when performing longitudinal studies over many months. It is preferable to perform repeated measurements within one season. Finally the problem of cleansing the skin or not before starting the measurements on the skin must be considered (the presence of excess sebum could influence the measurements). If preliminary cleansing is carried out, it must be done under standard conditions and followed by sufficient acclimatization time for the skin to recover.

The elaboration of valid guidelines by independent and unbiased expert groups and the publication of relevant and reproducible test results according to these guidelines, such as those suggested by the European Group on Efficacy of Cosmetics (EEMCO) group (12–16), should be encouraged for each type of technique to promote the recognition and acceptance of specific bioengineering measurements.

DISADVANTAGES

In this paragraph, we will give an overview of some problems when investigating the skin with noninvasive bioengineering methods.

Quoting Kligman: "A fool with a tool still remains a fool" (1); actually with the marvelous development of bioengineering techniques, one should quote: "A fool with a marvelous array of tools still remains a fool."

Single Limited Parameter

The noninvasive methods are by nature objective, quantitative, and generally investigator independent, and they can be calibrated and validated but are *narrow* based on a single physical modality of the propriety of the skin (2). As a consequence, each instrument is only able to detect and measure one single parameter of a complex skin structure, which is not sufficient for providing an overall clinical picture (7). For some investigations, it is necessary to combine two methods: the efficacy of an occlusive hydration cream can be evaluated using hydration and TEWL.

Measuring Units

The bioengineering instruments furnish as results either real physical units or arbitrary units.

Physical units are easily correlated with a physical phenomenon. For example: thickness of the dermis in millimeter; pressure applied in the suction method in millibar or Pascal, sebum quantity secretion rate in mg/hr, electrical capacitance in microfarad, etc.

Unfortunately many devices deliver nonphysical arbitrary units, which are much more difficult to correlate with a physical concept and to relate with other instruments. For example, laser Doppler and arbitrary flux/velocimetry units proportional to the speed of and the number of red blood cells. Comparing different instruments that deliver results expressed in *arbitrary units* is complex.

Calibration

The problem is that each company uses its own way to calibrate the device with its own proper standards. This procedure is not always transparent for the customers (sometimes the calibration is proprietary). Actually for many measuring techniques there is no *golden* universal standard, which can be used for standardization and validation for all instruments. Ideally, such a *golden standard* could be a simple artificial skin model whose properties are constant and known.

Claims Made by the Cosmetic Industry

When looking at the intensive advertisements and marketing done by the cosmetic industry, the very promising claims remain rather vague and are very difficult to substantiate by bioengineering methods. A few examples taken from the publicity in the cosmetic world: skin looks younger, rejuvenation of your skin, skin radiance, reenergizing the skin, the skin is invigorated, etc. How are we going to measure these claims? As an example, we will mention here the problem of the frequently mentioned cosmetic claim—skin tone or skin radiance.

Skin tone or skin radiance is an expression often used by the cosmetic industry in their publicity; more and more cosmetics are put on the market with the indication of skin radiance. The complex radiance is a reality that everybody is aware of, but difficult to describe. The evaluation of radiance is made by subjective visual observation either by the subjects themselves or by the investigators. Skin tone is the mirror of general good health, reflects emotional state (joy, sadness, stress, etc.), hormonal status (menopause), nutrition, fatigue, and age, and is also influenced by environmental factors (smoking, drinking, weather, etc.). Obviously we are faced with few objective criteria, and therefore a need exists for a bioengineering optical method of in vivo evaluation of the cosmetic radiance efficacy (17).

Mechanical Measurements on the Skin

The elastic and viscoelastic properties of the skin can be evaluated with different commercial devices: lateral torsion method (TorqueMeter®, Andover, U.K.) (18) and vertical suction method (DermaLab®, BTC-2000®, and Cutometer®) (19–24).

In the torsional method, the skin displacements in the horizontal plane can be small, and this lateral torsional movement involves only the epidermis and dermis (25). In the suction method, the mechanical stimulus is vertical to the skin surface. When applying a large probe aperture (1–2 cm) and working with a high negative suction pressure (400–500 mbar), the observed displacement involves epidermis, dermis, and may also include subcutaneous fat. Only the Cutometer presents a complete range of aperture diameter (2–8 mm diameter).

With all instruments, two type of curves can be obtained (see Fig. 1): the strain versus time curves, mode 1 (left, Fig. 1), which delivers elasticity, viscoelasticity, recovery parameters, and the stress-strain curves, mode 2 (right, Fig. 1), which allows to calculate the Modulus of

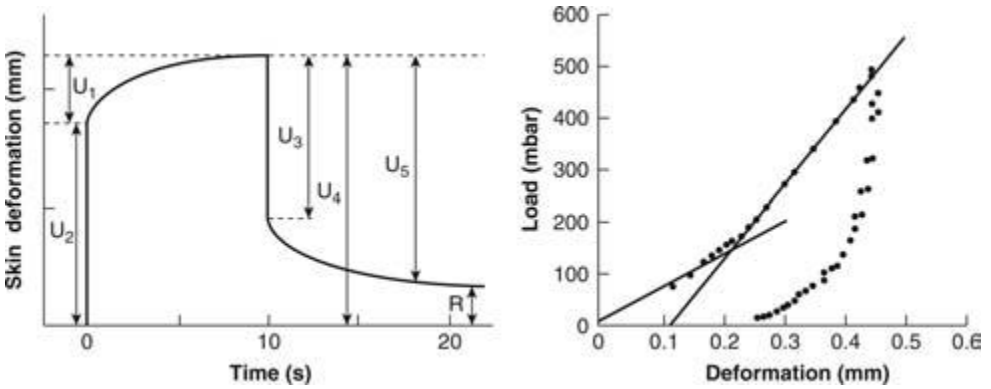

Figure 1 Strain-time curves (mode 1, *left*) and stress-strain curves (mode 2, *right*).

Young (firmness and stiffness). The Modulus of Young is normally not considered to be appropriate for a complex multilayer structure such as the skin (20). Both in vitro and in vivo uniaxial tension tests have shown that the amount of deformation grows steadily smaller so that the course of progressive extension cannot be represented by a straight line, but by a curve (Fig. 1, mode 2 in right side), (26). The calculation of Young's Modulus is complex because the skin shows a nonlinear stress-strain curve. However, this curve can be divided in three phases with more or less two linear portions. The first linear phase corresponds to the initial extension of the tissues at small loads, followed by the second linear phase corresponding to the stiffening of the dermis with increasing extension (24). The Modulus of Young can be either computed from the first linear phase (low stiffness) or from the second linear phase corresponding to higher stiffness. Considering the strain versus time curves (Fig. 1, mode 1), we are faced with the problem of the terminology of the different elastic and viscoelastic deformation parameters. A standardization in the terminology of these deformation parameters is strongly recommended (24,27). The development and further use of a universal in vitro calibration system using a simple skin model system (soft silicone polymers with known Modulus of Young and known viscoelastic properties) is strongly recommended in the future.

Hydration Measurements

Quantitative hydration evaluation of the upper layers of the skin, for example, horny layer and upper epidermis are numerous: electrical impedance and capacitance measurements (28), Fourier-transformed infrared spectroscopy with an attenuated total reflection unit, ATR-FTIR (29), and confocal Raman microscopy (30). The last two instruments, although they give quantitative data directly related to the amount of water present in the horny layer, are less used in routine clinical research due to the high price of purchase. Most routine hydration measurements are carried out using the electrical impedance/conductance properties: Dermalab (31) and Skicon® (Shizuoka-Ken, Japan) (32), impedance-based capacitive reactance: DPM Nova® (Portsmouth, U.S.A.) (33), or capacitance properties: Corneometer® (Köln, Germany) (34) and MoistureMeter® (Kuopio, Finland) (35), of an alternating electric current applied on the skin surface. It must be pointed out that the data of these instruments (electrical units or arbitrary units) are related to hydration, but not linearly proportional to the percentage of water present in the horny layer (28). Again, in vitro calibration can be carried out using simple model systems, such as cellulose filters impregnated with aqueous solutions and solutions of known dielectric or impedance properties.

Sensitive Skin

Despite the numerous different bioengineering instruments that are available and skin properties investigated, some dermato-cosmetic properties of the skin remain difficult to quantify. As an example, we would like to mention the concept of *sensitive skin*. The diagnosis of sensitive skin is defined by neurosensory hyperreactivity of the skin, and is essentially based on self-perceived sensations of people who report facial skin discomfort as stinging, burning,

and itching when their skin is exposed to some environmental factors (wind, sun, and pollution) or after application of topical products (hard water, soap, and cosmetics) (36). Epidemiological studies performed on large populations have shown that about 50% of women declare that they have self-perceived sensitive skin. Furthermore, the subjects with sensitive skin give a positive response profile, which is highly characteristic of a standardized *Sensitive Skin Questionnaire*. It appears from the literature that with the classical routine bioengineering devices it is very difficult to detect the presence of sensitive skin in subjects. Hydration, TEWL, and skin color are poorly correlated with sensitive skin (37). Only a very sophisticated device such as functional magnetic resonance imaging is capable to detect in the brain cortex specific sites involved with sensitive skin (36).

CONCLUSIONS

It is now obvious that noninvasive techniques have proven to be valuable tools for measuring objectively and quantitatively the biophysical and histological properties of the human skin; actually they are used more and more widely in dermatological departments for clinical diagnosis and therapy, and in pharmaceutical and cosmetic industries for safety and efficacy testing of topically applied product (38). Furthermore, bioengineering methods are becoming so sensitive that they are capable in well-designed cosmetic studies to show significant effects of topical products on the skin—effects that are not perceived by the consumers themselves. The noninvasive technology is harmless to the human volunteers and causes almost no discomfort. The eventual risks of bioengineering methods are concerning the substances applied on the skin: these topical ingredients could provoke irritant or allergic reactions. Most bioengineering instruments are commercially available at affordable cost. In addition, some of the recent devices are still experimental, developed by skillful engineers in research laboratories, and sometimes requiring experienced scientific operators. However, it is important to consider the limitations of the instruments used in bioengineering technology. These measurements are validated only if they are carried out under standardized conditions, if the devices have been calibrated, and if a certain number of precautions have been taken in account so that investigators in widely separated countries can obtain reproducible results and come to similar conclusions (1).

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77 The Current Regulatory Context in the European Union

Marleen Pauwels and Vera Rogiers
Department of Toxicology, Dermato-Cosmetology and Pharmacognosy, Vrije Universiteit Brussel (VUB), Brussels, Belgium

INTRODUCTION

Directive (Dir.) 76/768/EEC relating to cosmetic products (1) is a vertical legislation and every cosmetic product placed on the European market must fulfil its requirements. It would, however, be quite unrealistic to assume that this is a stand-alone piece of legislation that is not affected by other legal texts. In practice, Dir. 76/768/EEC forms part of a complex legislative process that was initiated more than 40 years ago to guarantee the free movement of goods within Europe while simultaneously ensuring the safety of the European citizens and their environment.

The current chapter provides an overview of the most relevant features of the Cosmetic Products Directive, after which the milestones depicted in Figure 1 are individually discussed in the light of their relevance to the cosmetic regulatory framework.

THE COSMETIC PRODUCTS DIRECTIVE

Definition of a Cosmetic Product

According to the European Commission Dir. 93/35/EEC, [Article 1], a cosmetic product is defined as *any substance or preparation intended to be placed in contact with the various parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition* (2). This definition gives an indication on the target site of application of a cosmetic product and on its allowed functions (3). Thus, products such as skin creams, lotions, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, soap products, shampoos, permanent waves, hair colors, toothpastes, and deodorants fall under the category of cosmetic products in the European Union (EU). More questionable product types such as suntanning preparations, antiperspirants, and antidandruff shampoos are also considered cosmetics within Europe, whereas this may differ in other parts of the world (4).

The Safety Prerequisite and Responsibilities

The current EU legislation on cosmetics literally states that *a cosmetic product put on the market within the Community must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use, taking account, in particular, of the product's presentation, its labelling, any instructions for its use and disposal as well as any other indication or information provided by the manufacturer or his authorised agent or by any other person responsible for placing the product on the Community market* [Art.2]. The responsibility to ensure that cosmetic products are safe for consumer use is placed upon the manufacturer or his authorized agent or by any other person responsible for placing the product on the community market (2).

A qualified safety assessor, holding a specified diploma (5) in the field of pharmacy, toxicology, dermatology, medicine, or a similar discipline, undersigns the safety assessment of the cosmetic product under consideration and thus takes responsibility for the safety of the product when applied under reasonably foreseeable conditions of use.

By means of a post-marketing surveillance system the EU member states are on their turn expected to take all necessary measures to ensure that only cosmetic products that conform to the provisions of Dir. 76/768/EEC and its Annexes may be placed on the European market [Art.3] (2). Nevertheless, the ultimate responsibility for the safety of a cosmetic product resides with industry.

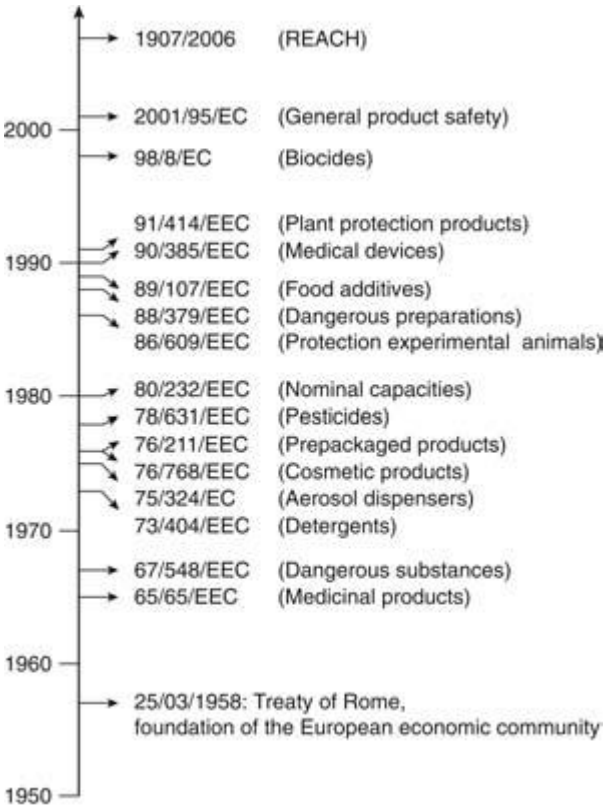

Figure 1 Overview of the major milestones in the EU chemical-related legislative process. *Abbreviation*: EU, European Union.

The Public Information Prerequisite

To optimally inform the consumer, every cosmetic product sold in the EU must contain the following information on its label [Art.6]:

1. name and address of the manufacturer or the responsible person for placing the product on the market within the EU;
2. nominal content of the finished product at the time of packaging (weight or volume);
3. date of minimal durability (products with a minimum durability less than 30 months) or an indication of the period of time after opening for which the product can be used without any harm to the consumer;
4. particular precautions to be observed in use, especially those indicated in the Annexes to Dir. 76/768/EEC;
5. batch number, enabling identification of manufacturing;
6. function of the product, unless evident;
7. a list of ingredients in INCI (International Nomenclature of Cosmetic Ingredients) in descending order of weight at the time they were added, unless they are present at a concentration below 1%, in which case they may be mentioned in any chosen order.

Moreover, the qualitative and quantitative composition of the cosmetic and the existing data on undesirable effects on human health resulting from use of the cosmetic product are enforced to be made easily accessible to the public by any appropriate means, including electronic means. Whereas the qualitative composition already features on the label (ingredient list mandatory), the quantitative composition is limited to "dangerous substances" according to Dir. 67/548/EEC (see section "Horizontal Provisions for the Protection of Animals").

The "Technical Information File" Prerequisite

For cosmetic products, the EU legislation does not foresee an extensive premarketing notification/authorization procedure involving a full toxicological dossier on the ingredients and the finished cosmetic product. Instead, the EU member states are charged with the

installation of a post-marketing surveillance system to check industry's compliance with the provisions of the Cosmetic Products Directive.

To this respect, Art.7a of the Cosmetic Products Directive imposes that the following information should be readily accessible to the member states' competent authorities (2,6):

1. Qualitative and quantitative composition of the product;
2. Physicochemistry, microbiology, and purity of the ingredients and the cosmetic product;
3. Manufacturing method;
4. Safety assessment of the finished cosmetic product;
5. Name and address of the safety assessor;
6. Existing data on undesirable effects on human health;
7. Proof of the effects claimed;
8. Data on animal testing.

The compilation of points (1) to (8) is commonly referred to as a cosmetic's technical information file (TIF) or product information requirement (PIR).

The Annexes to the Cosmetics Directive and the SCC(NF)P

Like the majority of EU Directives, Dir. 76/768/EEC is composed of the classical set of articles (definitions, responsibilities of the EU member states, safeguard clause, etc.), followed by a number of technical annexes. Five of them consist of ingredient lists:
Annex II: list of forbidden substances in cosmetic products;
Annex III: list of substances, which are not allowed to be used in cosmetic products outside the restrictions and conditions laid down;
Annexes IV, VI, and VII: lists of allowed colorants, preservatives, and UV filters, respectively, accompanied by their maximum levels and/or conditions of use in cosmetic products.

The content of these Annexes is regularly updated through amendments or adaptations to technical progress of the Cosmetics Directive. The cosmetic legislation charges the EU member states with the designation of a competent authority responsible for checking that every cosmetic product's composition complies with the provisions laid down in the above Annexes [Art.4] (2).

For the safety assessment of the ingredients appearing on the Annexes, the Commission is assisted by the Scientific Committee on Consumer Products (SCCP), previously called the Scientific Committee on Cosmetic Products and Non-Food Products intended (SCCNFP) for consumers. The SCCP forms part of DG SANCO[a] and owns the official mandate to provide opinions on questions concerning the safety of consumer products (nonfood products intended for the consumer). It is composed of independent scientists in the field of medicine, toxicology, pharmacy, dermatology, biology, chemistry, and other disciplines, collectively covering a wide range of expertize for this multidisciplinary committee (7). Together with the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), the SCCP provides the Commission with sound scientific advice needed when preparing policy and proposals relating to consumer safety, public health, and the environment. In addition, the Inter-Committee Coordination Group (ICCG), consisting of the chairs and vice-chairs of SCCP, SCHER, and SCENIHR, warrants harmonization of risk assessment and deals with questions, which are common to more than one committee, diverging scientific opinions and exchange of information on the activities of the three committees.[b]

In the EU, the safety of cosmetic ingredients is guaranteed by two operative channels, namely (8):

1. The safety evaluation of cosmetic ingredients to be taken up in the Directive's Annexes II, III, IV, VI, or VII, evaluated by the SCC(NF)P, and benefiting from an

[a]Directorate-General Health and Consumer Protection.

[b]http://ec.europa.eu/health/ph_risk/committees/committees_en.htm. Accessed February 2008.

extended physicochemical and toxicological data package as set out in the SCCP Notes of Guidance (7).
2. The safety evaluation of all ingredients present in finished cosmetic products is included in the product's TIF and carried out by a qualified safety assessor.

Since for substances not taken up in one of the Annexes to Dir. 76/768/EEC (1), no specific additional data requirements apply, the availability of data depends on data requirements and data accessibility measures laid down in the other legislation(s), with which these substances have to comply.

The SCCP specifically addresses questions in relation to the safety and allergenic properties of cosmetic products and ingredients with respect to their impact on consumer health, toys, textiles, clothing, personal care products, domestic products such as detergents, and consumer services such as tattooing (7,9). In this context, the committee also performs full risk assessments for candidate ingredients to be included in the Annexes to the Cosmetic Products Directive. The SCCP is not responsible for the safety assessment of cosmetic ingredients not taken up in the Annexes to the Cosmetic Products Directive (7).

Since 1997, the opinions of the SCCP and SCCNFP are made publicly available through the Committees' Web sites.[c]

The Animal Testing Ban for Cosmetics and Their Ingredients

Since the cosmetic field is often seen as a luxury area, posing no health benefits, being innocuous, and not needing any innovation, it turned out to be a fruitful battlefield for animal protection organizations, politicians, and parliament lobbyists to introduce an animal testing ban. Although, it was clear from the start that only a limited number of animals could be saved by banning animal tests for the safety of cosmetics and their ingredients (10), the "cosmetics case" became a remarkable example of how to introduce alternative methods into legislation in a politically driven and not scientifically driven way. The Sixth Amendment to the Cosmetic Products Directive for the first time introduced the concept of an animal testing ban on cosmetics and their ingredients. More specifically its Art.4 (1) stated that cosmetic products should not contain *ingredients or combinations of ingredients tested on animals after 1 January 1998 in order to meet the requirements of this Directive*. This statement was somewhat mitigated by the provision that *if there has been insufficient progress in developing satisfactory methods to replace animal testing, . . ., the Commission shall, by 1 January 1997, submit draft measures to postpone the date of implementation of this provision, for a sufficient period, and in any case for no less than two years, . . .* (2). The mentioned date of implementation was postponed twice (11,12).

Nevertheless, as a result of the limited progress in alternative method development and with the clear aim of pursuing the abolishment of animal testing for cosmetic products, the Seventh Amendment (6) to Dir. 76/768/EEC introduced explicit marketing and testing ban provisions for cosmetic products and their ingredients. More specifically, from 11 September, 2004, onward, animal experiments with finished cosmetic products are subject to an absolute ban, whereas a testing ban on ingredients or combinations of ingredients applies step by step as soon as alternative methods are validated and adopted, but with a maximum cutoff date of 11 March, 2009, irrespective of the availability of alternative nonanimal tests.

In addition, a marketing ban applies step by step as soon as alternative methods are validated and adopted in the EU legislation. This marketing ban will be introduced at the latest on 11 March, 2009, for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity, and toxicokinetics. For these specific health effects, the deadline of 11 March, 2013, is put forward, irrespective of the availability of alternative nonanimal tests.

Proposal for a Recast of the Cosmetic Products Directive

Quite recently, the European Commission published a proposal for a regulation on cosmetic products (13), the so-called recast of the 32 year-old Cosmetic Products Directive (1). This recast is meant to bring together the original directive with all its amendments, simultaneously introducing some substantive changes to the individual texts when

[c]http://ec.europa.eu/health/ph_risk/committees/sccp/sccp_opinions_en.htm, http://ec.europa.eu/health/ph_risk/committees/04_sccp/sccp_opinions_en.htm, and http://ec.europa.eu/health/ph_risk/committees/sccp/sccp_opinions_en.htm. Accessed February 2008.

incorporated. Since the recast is at the Commission proposal stage, it requires extensive discussions between the member states and within the European Parliament, implying that it will not remain unchanged. Nevertheless, it is useful to provide an overview of the major changes that are currently introduced. It should, however, be noted that the list below is not exhaustive and that it cannot be foreseen which of the provisions will actually be taken up in the final version of the regulation.

Moving from a Directive to a Regulation
One of the main goals for the recast being simplification of the administrative procedures related to the Cosmetic Products Directive, the text proposed aims at becoming a "regulation on cosmetics." European regulations have the advantage that they are binding in their entirety and are directly applicable in all member states, whereas directives need to be transposed into the national legal frameworks of the individual member states. With the 27 member states Europe currently counts, regulations automatically represent a major administrative simplification for the member states.

The articles of the original directive have been reorganized into chapters displayed in a logical order.

Introduction of a Set of Definitions
The recast aims at clarifying a number of issues for which legal uncertainty exists. Therefore, definitions for terms such as "manufacturer," "importer," "placing on the market," "making available on the market," "harmonised standard," "traces," "preservatives," "colourants," "UV filters," "(serious) undesirable effect," "repeal," and "withdrawal" are introduced in Art. 2, and some definitions of different cosmetic product types, such as "rinse-off product," "leave-on product," "hair product," "skin product," etc., are included in a preamble to Annexes II to VI. This preamble would replace the original Annex I to the Cosmetic Products Directive (1), which contains a non-exhaustive list of possible cosmetic product types.

One Single European Notification and a Strengthened Market Control
The proposed recast introduces a single centralized electronic notification of certain information concerning the product placed on the market. Instead of having to notify in every individual member state and needing to comply with all the national provisions (e.g., communication to poison control centres), the recast now foresees one single notification and one single poison control communication at the European level.

The member states are responsible for in-market control and in case of noncompliance, some specific possibilities for actions to be taken are mentioned in the recast (e.g., the introduction of penalties).

New Provisions for CMR Substances
Substances classified as carcinogenic, mutagenic or toxic to reproduction (CMR) category 1 or 2 according to the principles of Dir. 67/548/EEC (14) are actually prohibited for use in cosmetic products (6). The basic principle would remain unchanged, but the recast opens more possibilities in the sense that *there should be a possibility, in the exceptional case where these substances are legally used in food and no suitable alternative substances exist, to use such substances in cosmetic products if such use has been found safe by the SCCP*.

Introduction of Harmonized Standards
Throughout the text, reference is made to the use of harmonized standards. This implies that the Commission considers further development of European standards for analytical methods, claim substantiation, etc., enabling insurance of product compliance in these fields.

Clarifications on the Safety Assessment of Cosmetic Products
The TIF or PI(F) would be called the "cosmetic safety report." A newly created Annex I to the regulation would contain some guidance on the content of this report. A responsible person ensuring that the cosmetic safety report is kept up to date is to be designated.

The qualifications of the safety assessor are specified within the text and allow safety assessors also from outside Europe to sign the cosmetic product safety assessment.

"INCI" Becomes "Name of Common Ingredients Glossary"

The recast replaces the original INCI[d] list by the so-called common ingredients glossary. This glossary is described to contain the names of relevant cosmetic ingredients (~10.000), but not to constitute a list of authorized cosmetic ingredients. This is the same definition as was given for the INCI list, meaning that only the name has changed.

However, it must be emphasized that this new regulation on cosmetics is in a preliminary stage. It still needs to be discussed by the EU member states and the European Parliament, meaning that some adaptations are expected. This brings the possibility of a final version beyond 2009. The only certainty seems to be that all statements related to the animal testing ban as mentioned in the current cosmetic legislation (6) are precluded to be changed.

RELEVANT "VERTICAL" EU LEGISLATIONS

In parallel to the Cosmetic Products Directive, some other important legal milestones deal with the protection of human health with respect to specific types of substances. These so-called "vertical" legislations are depicted in Figure 2.

Although they all appear to function independently from the cosmetic legislation, there are some chemicals, which are regulated by more than one directive. Because of these intersections between the Cosmetic Products Directive and other vertical legislations, the following points address the relevance of each of them. Previously, we placed it in the light of data generation through the provisions of the above directives/regulations (8). Here, we focus on the existing intersections with the cosmetic field.

The Dangerous Substances Directive and REACH

Over the past four decades, chemical substances have been regulated at the European level by Dir. 67/548/EEC (14), its amendments and adaptations to technical progress. In first instance, this chemical legislation covers the listing and review of existing substances in the EU, together with the notification of new chemicals. Basically, a new chemical substance could only be produced within or imported into the EU after having received a favorable judgment from the EU member state's competent authority to which a full notification dossier has been addressed.

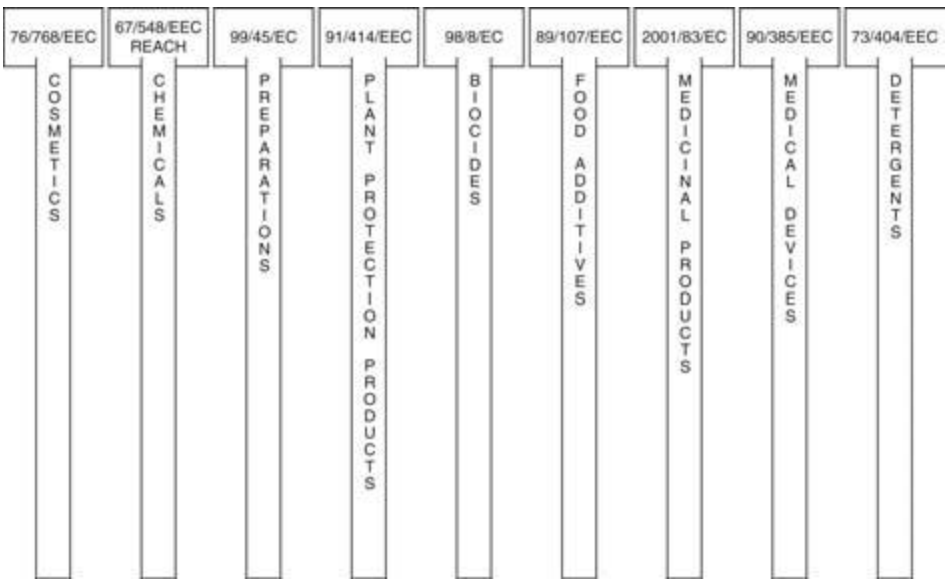

Figure 2 Schematic presentation of "vertical" cosmetic-related legislations in the EU. *Abbreviation*: EU, European Union.

[d]International Nomenclature of Cosmetic Ingredients.

In a second stage, the Dangerous Substances Directive covered the rules for classification and labelling of chemical substances in the EU. This means that not only test descriptions for physicochemical (Annex V, Part A), toxicological (Annex V, Part B), and ecotoxicological (Annex V, Part C) studies were provided, but also some explicit rules to translate the results from physicochemical and/or (eco)toxicological studies into a classification involving appropriate risk and safety phrases to be mentioned on the label (Annex VI). The classification and labelling principles of Dir. 67/548/EEC are still referred to in many other EU legislative texts.

The recently published EU Regulation No.1907/2006 (15) concerning the registration, evaluation, authorisation, and restriction of chemicals, commonly referred to as "REACH," introduces some major changes in the EU regulatory framework for chemicals, some of which are as follows:

1. The reversal of the burden of proof: Manufacturers and/or importers become fully responsible for proving and ensuring that their substances are safe for use, whereas previously the member states' competent authorities equally expressed an approval for the safe use of the substance under consideration [Recitals 18,25,29, Art.4] (15).
2. The creation of a European Chemicals Agency (EChA), established for the purpose of managing and in some cases carrying out the technical, scientific, and administrative aspects of REACH and to ensure consistency at community level in relation to these aspects [Art.75] (15).
3. Protection of experimental animals: REACH intends to reduce testing on vertebrate animals as much as possible by imposing data sharing, prohibiting duplication of animal testing, and the promotion of 3R[e]-alternative methods [Recitals 1,33,36,40,47,49, Art.13(2),15,25,26(3),27, Annex VI(1.4)]. Moreover, for the highest tonnage levels (>100 tonnes/yr), testing proposals need to be officially approved before the animal experiments are initiated [Recital 64, Art.22(1h),40] (15).
4. "PBT," "vPvB," and "CMR" substances and the substitution principle: REACH describes specific procedures as well for environmentally persistent, bioaccumulative, and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances, as for CMR substances [Art.14(4),40(1),58(3)]. Moreover, every application for authorization for such a substance must include an analysis of possible substitute substances or procedures as well as an analysis of their technical and economic feasibility [Recitals 12,70,72, Art.55] (15).
5. Enforcement of restrictions: Prohibitions on substances or restrictions on certain uses were previously imposed through Dir.76/769/EEC (16), its amendments, and numerous adaptations to technical progress. They will now be taken up by REACH through a faster and simplified procedure [Recitals 23,80,84,85, Art.68] (15).
6. The flow of information up and down the supply chain: Suppliers of a substance or a preparation must provide to their customers a safety data sheet including information about any potential hazard in detailed exposure scenarios. To enable suppliers to draw up correct exposure scenarios, downstream users will need to ensure a good upstream communication on potential usage patterns [Recital 56, Art.31,32,36,37] (15).

Although most cosmetic ingredients by definition are chemicals (17), they are exempted from the classification, packaging, and labelling provisions of the Dangerous Substances legislation and REACH. Nevertheless, good knowledge on these legal texts significantly helps to estimate data availability for a cosmetic ingredient (8) and to know its legal status as a chemical in the EU.

The Dangerous Preparations Directive

As early as 1973 and 1977, solvents, paints, varnishes, printing inks, adhesives, and similar products were identified as requiring special attention, and thus rules on these categories of preparations were laid down (18,19). However, divergences in national legislations on the remaining types of preparations still constituted a significant barrier to trade within the EU and led to the publication of an overall Dangerous Preparations Directive (20,21).

[e]Refinement, Reduction and Replacement.

Since "preparations" are defined as *mixtures or solutions composed of one or more substances* (21), numerous cosmetic ingredients fall under this category. Therefore, especially in negotiations with raw material suppliers, the cosmetic manufacturer benefits from a good understanding of the Dangerous Preparations Directive and its testing, classification, labelling, and confidentiality rules and provisions (8).

EU Legislation on Food Additives

Since food additives are intended to be ingested, this type of chemicals calls for a separate set of legal provisions and a risk assessment procedure. In Europe, food additives are regulated through a number of complementary directives (22–25) based upon the common principle that only those additives that are explicitly authorized and taken up in the official EU positive lists may be used and only subject to the specific restrictions laid down. In 2002, after a number of serious food crises in Europe (bovine spongiform encephalopathy, dioxins, and acrylamide), the general principles and requirements of food law were translated into a new regulation (26). The European Food Safety Authority (EFSA) was established to produce scientific opinions and advice for drawing European policies and legislation (inter alia the adaptations to the positive lists) and to support the European Commission, European Parliament, and EU member states in taking effective and timely risk management decisions with regard to food and food additives.

Since some cosmetic ingredients, such as flavoring and coloring agents, have also been accepted as food additives in the EU, their legal status in that field is useful to consult. In case the ingredients were found safe in the human food sector for daily ingestion, they usually make ideal candidates to be used in cosmetic products at comparable exposure levels (8).

The Biocidal Products Directive

Since biocidal active substances are intended to kill living organisms, they need to be accurately classified, labelled, and controlled to inform and protect the professional user and/or the general public. Therefore, the Biocidal Products Directive (27) deals with data requirements and risk assessments of active substances and ready-to-use end products. Herein, the classification and labelling provisions of the Dangerous Chemicals and Preparations Directives are taken over.

The intersection between the biocidal and cosmetic world mainly consists of preservatives used in cosmetics, which makes knowledge on the provisions of Dir. 98/8/EEC (27) relevant for that particular type of cosmetic ingredients (8).

The Medicinal Products Directive

The first version of a directive regulating the marketing of medicinal products in the EU was issued in 1965 (28). It has been repeatedly adapted and has been finally replaced by its current version in 2001 (29). The combination of the uncontested benefit and social value of medicines on the one hand and their potential side effects on the other hand leads to the necessity of extensive regulatory requirements.

However, in the EU, the use of medicinal active substances in cosmetics is strongly discouraged. A number of exceptions exist, but as a general rule, the intersection between active medicinal substances and ingredients allowed in cosmetics is kept very restricted (8).

The EU Legislation on Detergents

The legislation on detergents has been amended on several occasions until it was published in its final form in 2004 (30). Its focus resides on environmental aspects, viewing the chemical nature (many are anionic surfactants) of the substances concerned.

Cleansing cosmetic products typically contain different kinds of surfactants, which also form part of detergents. Therefore some knowledge on the detergents legislation may be of use, although to a more restricted level (8).

The Plant Protection Directive and the Legislation on Medical Devices

The EU Plant Protection Products Directive (31) and the Medical Devices Legislation (32,33) are taken up to complete the list, but are of inferior relevance for the cosmetic world. The intersection between cosmetic ingredients and chemicals involved in both fields is indeed very limited (8).

RELEVANT "HORIZONTAL" EU LEGISLATIONS

Besides the discussed "vertical legislations" coexisting in the EU, some horizontal directives also affect the regulatory background for cosmetics (as visualized in Fig. 3). In most cases, they are complementary to the Cosmetic Products Directive, but sometimes their provisions overrule the cosmetic legislation wherefore they certainly deserve to be mentioned.

Horizontal Provisions for the Protection of Animals

A directive commonly referred to by other pieces of legislation is Dir.86/609/EEC on the protection of animals used for experimental and other scientific purposes (34). Seeking to improve the controls on the use of laboratory animals in nearly all sectors, Dir. 86/609/EEC sets minimum standards for housing and care [Art.5] and the training of personnel handling animals and supervising the experiments [Art.7(1),14].

It also aims at reducing the number of animals used for experiments by requiring that an animal experiment should not be performed when an alternative method exists [Art.7(2)], and by encouraging the development and validation of alternative methods to replace animal methods [Art.23(1)]. The latter served as the basis for the Commission to set up the European Centre for the Validation of Alternative Methods (ECVAM) (35). Member states are imposed to collect statistical information on numbers and use of animals in experiments [Art.13].

It should be emphasized, however, that the scope of Dir. 86/609/EEC is restricted to (1) animal use in the framework of the development, manufacture, quality, effectiveness, and safety testing of drugs, foodstuffs, and other substances or products and (2) to the protection of the natural environment in the interests of the health or welfare of man or animal [Art.3]. Thus the fields of scientific research, education, and training and forensic research are not covered by this horizontal directive. Acknowledging this gap and to protect animals used in any procedure that may possibly cause pain, suffering, distress, or lasting harm, the Council of Europe published Decision 1999/575/EC (36). Herein, a number of conclusions of the 1986 European Convention for the protection of vertebrate animals used for experimental and other scientific purposes are officially approved. Basically, they defend the same principles as Dir. 86/609/EEC, but they additionally cover the neglected areas.

With the scientific progress made since 1986 and increasing political pressure on the development of alternative methods, a revision of Dir. 86/609/EEC was inevitable. Despite years of surveys and discussions on several aspects of the Directive such as scope, ethics, animal housing and care, statistical reporting, etc., allowing different parties to express their

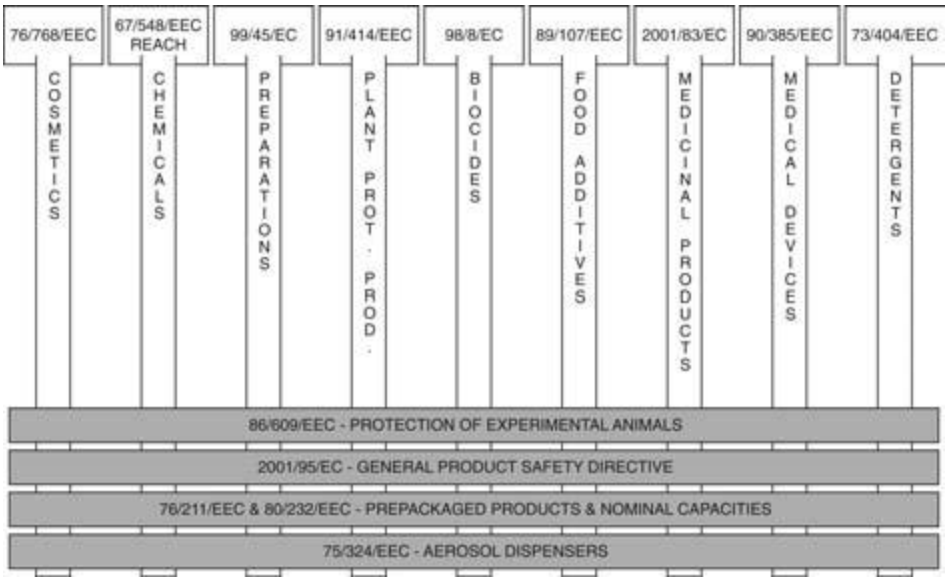

Figure 3 Schematic presentation of "vertical" and "horizontal" cosmetic-related legislations in the EU. *Abbreviation*: EU, European Union.

opinions and concerns, a generally revised version of the Directive is not yet available. The most recent developments can be obtained through the EU Directorate General Environment (DG ENV) Web site.[f]

General Product Safety Directive

The aim of the General Product Safety Directive (GPSD) (37) is to establish a coherent level of consumer protection for all consumer products on the internal market. Thus, it automatically covers many products, which are simultaneously regulated by the provisions of the vertical legislations mentioned under 1.4. The legal provisions of Dir. 2001/95/EC are, however, intended to be fully complementary while conveniently taking up consumer products falling outside the scope of other community legislation (e.g., lighters) (38).

Out of the numerous provisions of the GPSD, the following ones deserve special attention due to their relevance to the cosmetic field (38):

1. The basic principle of the GPSD is that only "safe" consumer products are allowed to be placed on the European market [Art.3(1)]. A safe product is defined as *any product which, under normal or reasonably foreseeable conditions of use including duration and, where applicable, putting into service, installation and maintenance requirements, does not present any risk or only the minimum risks compatible with the product's use, considered to be acceptable and consistent with a high level of protection for the safety and health of persons* [Art.2(B)] (37).

   At first sight, this completely corresponds with the provision of the Cosmetic Products Directive that a cosmetic product must not cause damage to human health (1). Nevertheless, it should be noted that the GPSD goes further by also covering, e.g., mechanical injuries caused by packaging of cosmetic products.
2. The GPSD describes active post-marketing activities for producers as well as competent authorities. The producers are obliged to perform sample testing, keep a register of complaints, and inform their distributors. They also need to alert the competent authorities. The latter are expected to take the appropriate steps to coordinate market surveillance and report every consumer product health risk into the harmonized European rapid exchange of information (RAPEX) system. This allows other member states to take necessary precautions with regard to similar products. The Cosmetic Products Directive includes a market follow up requirement as part of the information that should be kept readily available to the member states' competent authorities, but does not include any mandatory filing.
3. The GPSD gives the member states the authority to withdraw products from the market in case they are found unsafe. This provision is not taken up in the Cosmetic Products Directive, which means that for a withdrawal of a cosmetic product from the EU market, reference will be made to the GPSD.

EU Legislation on Prepackaged Products and Nominal Quantities

The term *prepackaged product* covers not only a wide range of consumer products, among which a large variety of foodstuffs but also cosmetics products. As early as 1976, Dir. 76/211/EEC related to metrological requirements for prepackaged products introduced the concept of mentioning the EU-harmonized e-sign on the product label in case the metrological requirements specified in the Directive were respected (prepackages between 5 g and 10 kg) (39).

For example, the tolerated error between the actual content (measured weight/volume of product) and the nominal quantity (quantity indicated on the prepackage, i.e., the weight/volume the prepackage is deemed to contain) is not allowed to be exceeded, the nominal quantity needs to be preceded by the e-sign and displayed in correct metrological units and marked in figures of predefined sizes depending on the overall size of the package. It must be mentioned that this Directive is currently under revision.[g]

[f]http://ec.europa.eu/environment/chemicals/lab_animals/revision_en.htm. Accessed February 2008.

[g]Details through http://ec.europa.eu/enterprise/prepack/metrol_requir/inmetrolog_requir_en.htm. Accessed February 2008.

In addition to the above-mentioned metrological requirements related to the use of the e-sign, Dir. 80/232/EEC imposes restrictions on the allowed nominal quantities for skin care and oral hygiene products, hair care and bathing products, alcohol-based cosmetics, deodorants, and personal hygiene products and talcum powders (40). However, this was considered to hamper the freedom of producers to provide goods according to consumer tastes and to hinder competition as regards quality and price on the internal market, wherefore Dir. 80/323/EEC is repealed.

From 11 April, 2009, onward, member states may not, on grounds relating to the nominal quantities of the package, refuse, prohibit, or restrict the placing on the market of prepackaged cosmetics (41).

EU Legislation on Aerosol Dispensers

In 1975, the Council of Europe drafted a Directive dealing with measures for the specific category of aerosol dispensers, independent of their content. The rationale was that viewing the presence of a gas compressed, liquefied or dissolved under pressure, aerosol dispenser's call for specific investigations. Capacities and volumes of individual powder, liquid or gas phases, flammability issues, coating of containers, and valve sealing are examples of aspects that need to be addressed before the European ∋-sign is allowed to be placed on the aerosol dispenser's label (42). Dir. 75/324/EEC (42) also covers deodorants and any other cosmetic spray.

However, it must be mentioned that this Directive is optional, meaning that member states can, under their national law, allow the marketing of aerosol dispensers not complying to Dir. 75/324/EEC, provided they do not bear the ∋-sign (43).

CONCLUSION

This chapter shows that the European cosmetic legislation foresees some clear duties, requirements, and prohibitions related to the placing on the market of finished cosmetic products. Simultaneously, however, it forms part of an extensive web of vertical and horizontal legislations intended to ensure the free movement and safe use of chemical-related substances within the EU. Basic knowledge on these individual legislative texts has become an essential tool to navigate within the European cosmetic world and understand some problems the concerned parties can be faced with today and in the near future.

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78 Trends in Cosmetic Regulations in the U.S.A.

F. Anthony Simion
Kao Brands Company, Cincinnati, Ohio, U.S.A.

INTRODUCTION

The regulatory environment for cosmetics in the U.S.A. is rapidly evolving. This is not due to changes in the U.S. regulatory framework for cosmetics; rather it is the effect of globalization. Globalization impacts cosmetic regulation in two, somewhat related, ways. Firstly, as manufacturers of both cosmetic raw materials and finished products try to sell their goods in multiple markets, they must abide by the regulations in each market. The U.S. is just one of the major markets in which companies sell their products. Other large, key markets include the European Union (EU), Japan, and China. The framework developed by the EU is becoming the model towards which many other countries and regions are gravitating. Thus, if an ingredient or product is to be compliant on a global, rather than on a national or even regional basis, it must take account of EU requirements.

Secondly, another impact of globalization is rapid communication. News stories about issues and problems are rapidly transmitted between countries and regions. Unfortunately, the Internet does not assess the accuracy or validity of the information. Furthermore, interested parties such as nongovernmental organizations (NGOs) and activists in different countries rapidly communicate with and learn from each other and determine what works and what does not. The NGOs have been very effective at molding public opinion, especially in Europe, and building coalitions that can change the regulatory environment at the legislative level.

The U.S. cosmetics industry through its trade association, the Personal Care Products Council (PCPC), is working to meet these challenges. The PCPC is working in parallel with trade associations in other regions, such as Colipa in Europe, to provide a balancing opinion as well as to influence the legislative and regulatory processes. This will become an even more important initiative in the future, if the U.S. cosmetic industry is to remain innovative and, to a large degree, self-regulating.

U.S. FEDERAL COSMETIC LAWS AND REGULATIONS

The underlying regulatory framework for cosmetic products at the federal level in the U.S.A. has remained unchanged for 70 years. The Federal Food, Drug, and Cosmetics Act of 1938 (1) defines a cosmetic as:

> . . .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.

It is the intent of the product, as defined by the claims made for its benefits, which determines whether the product is a drug or a cosmetic. One result has been the ability of marketers to sail closer and closer to this divide, making claims that suggest true physiological benefits, which would make them a drug, only to cleverly phrase the claim so it relates to appearance, making it a cosmetic. Frequently, these products are incorrectly termed "cosmeceuticals," which is a marketing term not a legal category. As one company makes a questionable claim, others rush to meet it and push the claim even closer to drug status. At some point, the Food and Drug Administration (FDA) recognizes that such advertising has crossed into drug claims and brings legal action or sends "Warning" or "Regulatory" letters. This happened in the mid-1960s with the "Wrinkle Remover" cases, and again in the late 1980s when the focus was on claims of antiaging and cell rejuvenation, and periodically since then. The cosmetic industry then recalibrates itself, learns where the new boundaries are, and

pursues other directions. The current interest in cosmeceuticals must be evaluated against the regulatory framework of only having drugs and cosmetics in the U.S.A. As there is no cosmeceutical category in the U.S., these products must fall into one of the two established statutory categories.

Another effect of the U.S. definitions of drugs and cosmetics is that a single formula can be either a drug or cosmetic, depending on the claims made. One good example is a soap containing triclocarban. If it is sold as a deodorant soap, it is cosmetic as deodorancy improves attractiveness. In contrast, the same formula being sold as antimicrobial soap, making disease prevention claims, is a drug (2). Another example is a clear antiperspirant gel made by Gillette in 1995, which was originally marketed as a deodorant. It made the claim of higher deodorancy than other deodorant products. Gillette successfully defended this claim with the National Advertising Division (NAD) of the Better Business Bureau on the basis of the antiperspirant technology being more effective at reducing body odor than that used in deodorants, which do not contain aluminum salt (3). The one exception to that general rule is where the included therapeutic ingredient, such as penicillin, is so well known that its very presence in a product would imply therapeutic, i.e., drug benefits (2).

There is no premarketing review or approval required before selling a new cosmetic in the U.S. Thus the FDA only regulates cosmetic products once they have reached the marketplace. Last year, in their review of nanotechnology, the FDA confirmed that this approach was appropriate for cosmetics (4). The FDA does have the ability to exclude ingredients that they believe to be harmful. In the past they have declared that the presence of halogenated salicylanilides such as tribromsalan (TBS, 3,4′,5-tribromosalicylanilide) or hexachlorophene in a cosmetic would result in an adulterated product. In 2005, the FDA issued a "guidance" to the effect that cosmetic products containing α-hydroxyl acids (AHA) should carry the sun burn alert, unless the manufacturer had data that showed that the increased AHA-induced UV damage to the skin would not occur (5).

There are many consumer products that carry both drug and cosmetic claims and are therefore governed by both sets of regulations. In practice, as the drug regulations are more stringent for many aspects including manufacturing (Good Manufacturing Practices, GMP) and adverse event reporting, these combination products are effectively regulated as drugs. Many of these combinations are over-the-counter (OTC) drugs, and as long as the monograph requirements are met, preapproval to enter the marketplace is not required. OTC regulations continue to slowly evolve. Some of the monographs that impact personal-care products have been finalized, such as antiacne and antidandruff. Others are still at the tentative final stage, such as antimicrobial. The monograph for sunscreen products is still a work in progress. In August 2007, the FDA proposed changes to the monograph related to UVA testing, labeling, and use instructions (6). It is not clear when these amendments will be finalized.

Like the personal-care industry, the FDA has recognized the increasing concern of some of the general public regarding the safety of cosmetics. In 2004, The Environmental Working Group (EWG) petitioned the FDA to take a more active regulatory role, including the preapproval of cosmetics before they were marketed. The FDA rejected the petition, believing that it already had sufficient authority to regulate cosmetics and ensure their safety (7). This is similar to the position that the agency took on nanotechnology. Since then, the FDA has strengthened the voluntary registration of manufacturing premises and ingredient statements, which has existed since the 1970s. The voluntary annual reporting of adverse events was discontinued in the mid-1990s and has not been reintroduced, except for those that are "Serious and Unexpected." At the same time the personal-care industry has proactively introduced a program, the Consumer Commitment Code, to make the safety assurance process for cosmetics more complete and transparent. It is described in more detail in the section "U.S. Cosmetic Industry's Response to the Changing Regulatory Environment," and is in part based on the work of the Cosmetic Ingredient Review (CIR), a board of independent dermatologists and toxicologists that reviews the safety of cosmetic ingredients. The FDA has a nonvoting liaison status with the CIR.

Over the last 40 years, several legislators have attempted to increase the role of the federal government, especially the FDA, in the regulation of cosmetics and their safety. The U. S. cosmetics industry has successfully remained, mainly, self-regulatory by continuing to develop comprehensive safety programs that meet the government's and the public's expectations, while maintaining an excellent safety record in the marketplace.

The FDA is not the only federal agency that has jurisdiction over cosmetics and the personal-care industry. The Consumer Product Safety commission regulates some aspects of product labeling under the Fair Packaging and Labeling Act (FPLA). The Bureau of Alcohol, Tobacco, and Firearms (ATF) also regulates the packaging and labeling of those cosmetic products that contain ethanol (8). The Federal Trade Commission (FTC) has jurisdiction over the fairness of advertising, especially as it relates to false or misleading claims. Recently, the FTC has become more active in ensuring compliance with advertising rules for both cosmetics and dietary supplements, especially in the areas of weight loss and hair growth where there has been a long history of questionable claims.

STATE LAWS AND REGULATION OF COSMETICS IN THE UNITED STATES

For many years, individual states in the U.S. have had laws and regulations that impact cosmetics. Primary examples of this are from California, where the volatile organic compound (VOC) regulations have changed the composition of many cosmetic products such as hairsprays. The California Proposition 65 limits the level of potential carcinogens and reproductive toxicants that a person can be exposed to each day; otherwise warning labeling is required. Such regulations can impact personal-care products across the U.S. It is difficult to control distribution of a product once it leaves the manufacturer's warehouse and reaches mass merchandisers. Therefore, many manufacturers follow the requirements of California across the entire U.S.A.

Recently, California passed the Safe Cosmetics Act (2005) (9). This requires manufacturers to disclose to the State of California the intentional addition of potential carcinogens and reproductive toxicants. These would be posted on a Website that the public can access. Currently, the State of California is working with the various stakeholders to determine the best way to implement the law. We have yet to see the law's impact on the cosmetics industry.

Frequently, other states have discussed new cosmetic laws, but most have not been enacted into law. For instance, Massachusetts is considering a law saying that one cannot sell a cosmetic product with an ingredient that the CIR has said is unsafe. In the first year, companies will have the opportunity to remove the unsafe ingredient; the following year the product will be considered adulterated. Again, modern distribution systems for their products prevent companies from segregating products and preventing their sale in a specific state. Hence, such a law will have national or at least regional impact in the U.S. This does not take account of any publicity that may arise when a product cannot be sold in a specific area because of safety concerns.

Obviously, the personal-care industry prefers to have a single set of laws and regulations to follow, rather than separate requirements in each state. Furthermore, since many of the laws related to product safety utilize information and analysis published by panels or committees of experts, industry is trying to ensure that a few lists of the highest scientific quality are used as the basis of the regulations.

IMPACT OF EU LAWS AND REGULATIONS ON U.S. COSMETICS INDUSTRY

Although they do not have the force of law in the U.S., EU (and Canadian) cosmetic regulations are having a great impact on the development of raw materials and cosmetic products in the U.S. This is because cosmetics manufacturers want to be able to develop global formulas or, at least, ones that can be sold in a major market of the U.S. and EU. To do this, the products must be compliant with both sets of cosmetic regulations, and in this way, the EU impacts cosmetics produced in the U.S. Furthermore, Canada and Mexico are beginning to take more account of EU regulations as they develop their own. In this way, a Pan-North American personal-care product, will be impacted by the EU, even if the product is not intended for distribution in Europe. Indeed, Association of South East Asian Nations (ASEAN) has modeled their new cosmetic regulations on the EU.

For ingredient safety, there has already been a degree of harmonization. The science of toxicology is the same around the world. Thus, the criteria in evaluating safety that are applied by the advisory bodies in the U.S. (CIR) and in the EU (the scientific committee on cosmetic

products, SCCP) tend to be similar. This contrasts with labeling regulations where there is far less commonality among different regions on the basis of language requirements, as well as national sensibilities and expectations around product performance claims. The exception to this is the ingredient declaration, where the INCI nomenclature is becoming the global standard.

In the future, the regulation burden on cosmetic ingredients will increase in the EU with the introduction of the REACH (Registration, Evaluation, and Authorization of Chemicals) legislation and the animal testing and marketing ban, which commences for single dose methods in March 2009. It is not clear whether the effect of REACH will be as great in the U.S. as it will be in Europe. Many raw materials will have to be REACH compliant; they will have to meet EU regulations to be sold in Europe, and precluding the EU market will significantly reduce ingredient manufacturers' return on their investments. The same will hold true for the animal testing ban and its impact on the development of new raw materials in the cosmetic industry. Even with fragrances, EU regulations can impact formulas sold in the U.S. The EU requires labeling in the presence of fragrance ingredients that are putative allergens when they exceed specific thresholds. Many cosmetic manufacturers want to avoid such labeling for, at the minimum, it can significantly lengthen the ingredient statement. If a cosmetic manufacturer is going to have a global fragrance for the global product, again, EU regulations will have an impact.

In the past, the attempts to harmonize cosmetic regulations at the governmental level have been unsuccessful. However, industry pressures such as global economy of scales have led to a de facto harmonization of ingredients in products. Currently, the International Committee on Cosmetic Regulations (ICCR), which includes industry as well as governments and other stakeholders, is working to harmonize many of the tests, methods, and procedures so single methods and assays can be used across different jurisdictions and regulatory frameworks. Issues discussed at their first meeting (September 2007) include GMP, ingredient statements/INCI, nanotechnology, in-market surveillance as well as animal testing and alternative methods. A summary can be found at http://www.cfsan.fda.gov/~dms/cosiccr.html.

U.S. COSMETIC INDUSTRY'S RESPONSE TO THE CHANGING REGULATORY ENVIRONMENT

In the U.S., the cosmetic industry association (PCPC) is responding to the pressures of the activists and others concerned with the safety of cosmetics. Traditionally, the Council, when it was known as the Cosmetic Toiletry and Fragrance Association (CTFA), focused on its relationship with the U.S. federal and state governments. However, in the last five years, the NGOs in the U.S. have been having a greater impact on state legislators and in the court of public opinion. An example of the former is the pressure that was exerted in California that resulted in passage of the Safe Cosmetic Act (2005). Seeing this trend and recognizing what has already happened in the EU could portend what happens in the U.S.; the U.S. cosmetic industry is becoming more proactive in meeting this challenge. It has realized that it needs to increase its efforts to provide accurate information to the public and the press and use this as the starting point in influencing public opinion. The result is several initiatives from the council, which include

- The Consumer Commitment Code: industry is working to make the safety assessment process more transparent to the press and public in general. The code emphasizes that cosmetic manufacturers have a solid scientific basis for the safety of both the ingredients that they use and the final product.
  - For ingredients, it is recommended that companies use the assessments of expert authoritative bodies such as the CIR, FDA, SCCP, or NICNAS (Australia's National Industrial Chemicals Notification and Assessment Scheme) as the basis of the safety assurance process. Indeed, ingredients that the CIR finds to be unsafe should be excluded from products. Ingredients with a CIR-"insufficient" data finding should only be used if the company has enough scientifically valid data to support their safe use.

- Serious and unexpected adverse events (reactions) should be reported to the FDA in a timely manner.
- The FDA can make written requests to review the data that form the basis of a product's safety assessment.

- The council has set up a Website to give accurate information to the press and public in a way that is easier for them to understand. Its address is www.cosmeticsinfo.org.

These efforts are a start in the industry's goal to remain self-regulating. To do this successfully will require that industry effectively manage attacks from the activist NGOs. They have been active and effective in the EU. Their counterparts in the U.S. have been following their lead. The U.S. industry must watch what is happening in the EU, because with the rapid communications across the Atlantic, those regulations will be proposed in the U.S. very quickly.

CONCLUSIONS

Although the legal framework for cosmetic regulation has not significantly changed in the U.S. for 70 years, in practice, the U.S. regulatory environment is evolving rapidly. With globalization of raw materials and cosmetic formulas, the U.S. cosmetic industry is impacted by regulatory regimes from the different regions in which the ingredients and products are sold. This is especially true for the framework developed in the EU, which appears to be becoming the international benchmark. Many countries and regions are following the EU's model, or at minimum, incorporating some of the EU's approaches in their regulatory framework. Therefore, it is important for U.S. companies and industry to work closely with, and support their EU counterparts, as the Europeans try to influence their legislative and regulatory processes.

Green and other activist groups have been more politically influential in Europe than they are in the U.S. However, in the last few years, the U.S. NGOs have become more vocal and successful in influencing public opinion and legislators. This resulted in the passage of the California Safe Cosmetics Act (2005). The U.S. personal-care industry has not been willing to cede the "court of public opinion" to the activists. The PCPC (industry association) has developed a website (www.cosmeticsinfo.org) to provide accurate information to the public, and especially to the press. Additionally, the PCPC is working to make the product safety assurance process more transparent, through the introduction of the Consumer Commitment Code. In contrast, the FDA is not changing its approach; instead it is using the current regulatory structure to respond to scientific advances such as nanotechnology and to pressure from the activist NGOs.

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