Practical Aspects of Cosmetic Testing

How to Set up a Scientific Study in Skin Physiology
The idea of “practical guidebook” was born after a hands-on workshop where several participants asked about a recommendation for reading of practical aspects. The current handbooks offer a plethora of scientific overviews and cover the broad spectrum of noninvasive measurement devices for cosmetic skin testing. However, practical aspects of performing cosmetic aspects are not always covered. Also, the published guidelines do not always cover the day-to-day questions arising during the preparation, performance, and evaluation of clinical studies. The aim of the present book is to provide practical guidance for scientists, especially those new in the field or those who face practical problems with their studies. New lab members should have a useful first-to-read source at hand.

I would also like to honor some “corner stones” in the development of modern biophysical instrumentation such as Rony Marks, Harvey Blank, Pierre Agache, Gary Grove, Jorgen Serup, Howard Maibach, Peter Elsner, Enzo Berardesca, Albert Kligman, and the most innovative company in the field, Courage & Khazaka. Some of them have played an important role in the development of my personal career.

I would like to thank all authors of this book. Without their dedicated contributions this project would not have been possible. Special thanks should go to Ms. Blasig, from Springer. She supported this project during its entire process with enthusiasm and dedication.

Albert Kligman had a saying, which I would like to keep in mind when starting and advancing in the field of biophysical assessment of skin functions: “A fool with a tool is still a fool”. Thus, the brain of the scientist should be active when performing and analyzing measurements. Hopefully this book will fill the gap between the detailed scientific textbooks, original and review publications in international journals, and the practical hands-on training that needs to be integrated in the education of young scientists in cosmetic testing.

Berlin, October 2010

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In the era of evidence-based medicine we are witnessing a growing demand for standardization and objective assessment of different physiologic and pathologic conditions as well as for monitoring the efficacy of different therapeutic modalities. The same trend is seen for cosmetic studies. A great number of devices for efficacy testing of cosmetic products have been invented and developed in the past decades. However, a lot of questions remain open when proving efficacy and safety of cosmetic products:

- What parameters and devices are suited to test specific claims?
- How to perform the measurements in practice?
- What should be the test population and what study protocol is most appropriate?
- What environment-, subject-, and instrument-related conditions should be considered?
- What are the regulatory and ethical aspects of cosmetics testing?

This book is intended in the first line for answering the above-stated questions. It will be of practical interest especially to the “new-bees” in the field of cosmetic research, including cosmetic scientists, cosmetic chemists but also dermatological researchers of functional aspects (clinical assessment of disease activity and skin physiology), pharmacists, biologist, and biochemists. Furthermore, professionals working in clinical study centers and contract research organizations (including project managers, study nurses, and physicians) will benefit from the lecture of the present book. The targeted practical point of view together with the “step-by-step” approach when planning and performing cosmetic testing are the main advantages of this manual in comparison to former books in the field.

Skin physiology assessment is moving rapidly from a descriptive approach to a deeper understanding of biophysical and biochemical processes in the epidermis, namely epidermal barrier function, stratum corneum hydration, and the underlying regulated processes. The research with noninvasive biophysical measurements, formerly called bioengineering methods, offer now reliable and reproducible approaches for product testing in the cosmetic industry as well as in basic research. Herein, basic information on technical and legal aspects on cosmetic testing is presented. The authors give insight into very practical aspects of basic skin physiology and the assessment of skin functions in controlled studies. The last (and the broadest) part of the book is dedicated to specific typical examples of test
settings. Of course, a book dedicated to address basic aspects cannot cover the entire spectrum of possible test approaches. The most frequently used endpoints are described.

Research with non or minimal-invasive devices to study skin physiology and the effect of cosmetic products enters in its 5th decade. We are now using the “fourth generation” of instruments. It started in the early 1970s with the assessment of stratum corneum hydration, epidermal barrier function (by measuring transepidermal water loss), and skin mechanical properties. The instruments were often the size of a cupboard or table. Individual instruments were built in the labs and most of the time only prototypes were manufactured that never made their way to wide distribution and general acceptance.

These “first generation” individual instruments were often designed by cosmetic companies for testing their specific product claims. The “second generation” instruments were stand-alone devices, significantly smaller and cheaper. They were the first ones built on larger scales, thus accessible for broader public and academic institutions (Fig. 1).

The “third generation” of measurement devices consisted of instruments attached to a PC via a central-unit allowing direct storage of measurement values. Some manufacturers minimized the measurement technology in such a way that the device was actually in the handheld itself. A skin physiology lab could now fit into a small suitcase. The “fourth generation” is now available with easy to perform calibration check. State of the art instrumentation allows good validation studies and interlaboratory comparisons. The next step (maybe the “fifth generation”) should be to transform the measurement units, today in most cases arbitrary units (AU), to SI units.

The work on standardization led to the publication of several guidelines (see Chap. 2.4. by Pierard et al.) Unfortunately, the working group of European Group for Efficacy Measurements on Cosmetics and other Topical Products (EEMCO) is no longer in place and thus no update on these guidelines will be available in the near future. Maybe, widely accepted standard operation procedures (SOPs) will be implemented or guidelines will be published that are accepted by regulatory authorities. Systematic reviews on the evidence (EBM) for different methods or compounds might help to improve the standards in cosmetic testing. Another step would be to harmonize training courses and maybe to install training certificates based on standardized training sessions. There is still a lot of work to
do, but we have reliable instruments and knowledge available to perform good scientific studies. Rigorous scientific planning together with accurate data analysis will ensure and enhance the credibility of cosmetic testing, especially if some of the standards already in place for testing of topical drugs (e.g., comparing to placebo/control, sample size calculation, and submission to authorized ethic comities) are implemented in the cosmetic study protocols. Today, consumers are well informed not only via the internet, but also due to the easily accessible information especially by the big cosmetic companies. Thus, claims have to be substantiated with good science and controlled clinical studies. Noninvasive instrumentation is a cornerstone of standardized clinical testing.

The present book provides basic knowledge on how to plan, perform, and evaluate scientific studies. The authors are recognized experts in the field and describe in comprehensive chapters the practical aspects of noninvasive measurements. The first part of the book is dedicated to regulatory aspects of cosmetic testing including guidelines, ethical aspects, and claim support. The second part deals with the general aspects of cosmetic studies, namely requirements of the testing laboratory, testing staff, populations, study design, and the reporting of the study outcomes. The third part is dedicated to some typical examples of test settings including efficacy claim studies for moisturizers and emollients, antiaging and antiwrinkle products, antiperspirants and deodorants, and cosmetics for impure skin; and assessment of hair morphology, skin color, and others.

Getting acquainted with the good practice in cosmetic testing would be helpful to the reader not only for better practical performance of a study, but also to interpret and evaluate the strong and weak points of other investigators’ research.

The book should guide into good planning, careful performing, and critical interpretation of cosmetic studies. Of course, reading does not replace hands-on training and personal experience.
Part I

Legal Aspects of Cosmetic Testing
In general, the regulatory basics for cosmetics are different in different countries. Even the classification rules defining what a cosmetic is differ between countries. A product that is classified as a cosmetic in one country may be classified as a drug in another country. This has implications for the testing of cosmetics. Depending on which country the testing is...
performed and/or the test product is (to be) marketed, different specific testing may be required, desirable and/or allowed. The following chapter gives a brief introduction on the regulatory aspects of clinical testing of cosmetics. However, this chapter serves for informational purposes only and does not provide legal advice.

1.1 Comparison Between General Cosmetic Legislation in Europe and Other Countries

The differences in regulatory basics for cosmetics in different countries are numerous, complex, and may be confusing for the regulatory layman. Fortunately, there are also some universal similarities at least for the major market economies:

- The marketer has full responsibility for the safety of products – the expected manner of use must not be harmful for the health of the consumer. No premarket approval by the authorities is necessary.
- In-market control of the cosmetic products is performed by the respective authorities (in different ways).
- Any distribution channel for the product may be used (shops, mail order etc.).
- Claims and other information given to the consumer regarding the cosmetic product must not be misleading.
- For ingredient declaration on the packaging, the INCI (International Nomenclature of Cosmetic Ingredients) system is widely used and required.

Furthermore, the cosmetics regulation frameworks may be classified into two large groups:

1. Regulation systems with broad definitions of cosmetics. These employ extensive lists with restrictions for specific ingredients as well as positive lists for allowed ingredients and require safety data to be available.

This framework model roughly describes the EU cosmetics regulation. Considering its success in regulating cosmetic product safety on the one hand and allowing innovation of cosmetic products on the other, and keeping in mind the global importance of the European cosmetic product market, it is not surprising that many emerging countries have modeled their cosmetic regulation systems after the European example. In fact, the cosmetic regulations of the ASEAN countries (Indonesia, Malaysia, the Philippines, Singapore, Thailand, Brunei, Burma (Myanmar), Cambodia, Laos, and Vietnam), the Mercosur countries (Brazil, Argentina, Paraguay, Uruguay), the Andean Pact countries (Bolivia, Colombia, Ecuador, and Peru) as well as South Africa are very similar to the respective EU regulations (except regarding the ban on animal testing, which up to now remains a European “specialty”).

2. Regulation systems with narrow definitions of cosmetics. These impose few specific restrictions regarding ingredients and few requirements regarding available safety data for cosmetics. However, depending on the claims made, or depending on contained ingredients for which a therapeutic effect is known, many products that may be classified
as a cosmetic within the former regulation systems may be classified as an over-the-counter (OTC) drug here. This framework model roughly describes the cosmetics regulatory system in the USA.

The regulatory systems of two further major markets, Japan and Canada, fall between the two antipode systems described above. The Japanese system also works with positive and negative ingredient lists, but features a third, intermediate category of products, the quasi-drugs. Quasi-drugs are defined as articles that are used for certain purposes/indications/claims and are restricted to a list issued by the Ministry of Health and Welfare Japan (MHW). The Canadian system is similar to the US system, but with longer restriction lists (“Cosmetic Ingredient Hotlist,” modeled after the negative lists valid in the EU).

The cosmetics regulatory system of China, a market that is of increasing interest, is somewhat different, but currently under review and may change considerably in the future. Currently, the regulation system (which is integrated in the drug regulation) differentiates between “ordinary” and “special cosmetics.” To put it simply, the former category consists only of decorative and cleansing cosmetics, and the latter category of cosmetics that have a function that goes beyond that. Furthermore, cosmetics are also handled differently depending on whether they are produced by a domestic Chinese manufacturer or imported from outside of China: Imported cosmetics must undergo a rather lengthy and complicated premarket registration and approval process, requiring strictly specified safety testing and acquisition of several licenses involving several national and regional government bodies. Furthermore, all testing has to be done in China. These obstacles have been criticized by some representatives of western economies as being discriminatory. It will be interesting to observe if this will change in the future.

Lastly, India is also a large market that was of less interest to major cosmetic manufacturers in the past, probably because of the low average income of the population. However, it is becoming increasingly important considering its economic growth. Its cosmetic regulatory system is completely integrated in its drug regulatory system (its origins dating back to the 1940s), with rather narrow definition of cosmetics similar to the USA system.


1.2 Recent Changes in European Cosmetic Regulation

On March 24, 2009, the European parliament recast (with a few amendments) the fundamentals of European cosmetics law, the European Cosmetics Directive 76/68 EEC, which originated in 1976 and was updated and amended many times until today. The original directive was a European guideline which had to be translated into national law by each of the EU states. This led to a few differences between the cosmetics regulations in the EU countries, for example, in the “positive lists” containing allowed ingredients (colorants, preservatives, UV filters).

The present recast is a directly effective legal act, eliminating such differences. Furthermore, it integrates all former amendments and includes some clarifications and
definitions, for example, a glossary on legal terms used. For the first time, it is specified which safety tests and assessments are to be done for the safety dossier that is to be kept on file at the manufacturer. The specifications of the safety dossier were modeled on the recommendations by the Scientific Committee on Consumer Products (SCCP) on safety testing of cosmetics, which up to now were required only for new ingredients to be added to the positive lists. For the first time, the use of nanomaterials is specifically regulated. Furthermore, the recast stipulates EU-centralized premarket submittal of basic information on the product in order to facilitate and strengthen postmarketing surveillance and “cosmetovigilance.”

Recast of the European Cosmetics Directive:
For tracking of the legislative status this link may also be checked:

1.3
Important Weblinks

1.3.1
European Union

Consolidated version of the seventh amendment to the European Cosmetics Directive:
SCCP central website:
Important SCCP guidelines/opinions:
Colipa (European Cosmetics Association) central website:
http://www.colipa.eu
German Cosmetic, Toiletry, Perfumery and Detergent Association (IKW):
http://www.ikw.org
General information for marketers:
German Federal Institute for Risk Assessment (BfR):
http://www.bfr.bund.de/cd/template/index_en

1.3.2
USA

Food and Drug Administration (FDA): Information for Cosmetics Industry, “Highlights”:
http://www.cfsan.fda.gov/~dms/cos-ind.html
http://www.cfsan.fda.gov/~dms/cos-toc.html

The Personal Care Products Council (formerly the Cosmetic, Toiletry and Fragrance Association (CTFA)):
http://www.personalcarecouncil.org

### 1.3.3 Canada

Health Canada, centralized information on cosmetics regulation:

Cosmetic Ingredient Hotlist:

### 1.3.4 Japan

Ministry of Health, Labour, and Welfare (MHLW):
http://www.mhlw.go.jp/english/topics/cosmetics/index.html

No official translation of the Pharmaceutical Affairs Law (PAL) available, unofficial version:
http://www5.cao.go.jp/otodb/english/houseido/hou/lh_02070.html

Japan Cosmetic Industry Association (JCIA), available only in Japanese:
http://www.jcia.org/

### 1.3.5 Mercosur Countries (Examples)

Argentinian National Administration of Pharmaceuticals, Food and Medical Technology (ANMAT), search also for Resolución 155/98 del 13/03/98:
http://www.anmat.gov.ar/cosmeticos.asp

Brazilian National Health Surveillance Agency (ANVISA), search also for Resolução nº 79, de 28 de agosto de 2000:
http://www.anvisa.gov.br/e-legis/

### 1.3.6 ASEAN Countries (Example)

Singapore Health Sciences Authority (HSA):
1.3.7 South Africa

South African Government Information, search for “FOODSTUFFS, COSMETICS AND DISINFECTANTS ACT, 1972 (ACT NO. 54 OF 1972)”:  
Cosmetics, Toiletry and Fragrance Association of South Africa (CTFA):  
http://www.ctfa.co.za/

1.3.8 China

State Food and Drug Administration (SFDA):  
http://eng.sfda.gov.cn/eng/  
General Administration of Quality Supervision, Inspection and Quarantine of P.R.C. (aqsiq)  
http://english.aqsiq.gov.cn/

1.3.9 India

Central Drugs Standard Control Organization (CDSCO):  
http://www.cdsco.nic.in/html/law.htm  
http://cdsco.nic.in/html/Copy%20of%201.%20D&CAct121.pdf

1.4 Cosmetic Safety Testing

This section mainly addresses the situation regarding cosmetic safety testing in Europe. However, in the other major markets most aspects apply accordingly. The most important difference may be the different views on ethical aspects regarding the availability of animal data prior to human testing. In Europe, such data may be replaced by alternative (nonanimal) methods, animal data in some cases even being impossible to obtain due to the animal testing ban. In contrast, in other major markets such animal data is required prior to testing in humans.

The most important property of a cosmetic is its safety, which must be checked prior to marketing a cosmetic product (EU Cosmetics Directive).

In the recast of the EU cosmetics directive as well as in guidelines by the SCCP and Colipa, the product safety properties that should be addressed and documented are listed.

Already in 1999, the SCCP issued a “Guideline on the use of human volunteers in compatibility testing of finished cosmetic products” providing the basic principles. Weblink:
These were based on the declaration of Helsinki, Good Clinical Practice principles and national regulations regarding human studies. Helpful in this regard are also the “Notes of guidance for testing of cosmetic ingredients for their safety evaluation” issued by the SCCP, which are updated occasionally.


In these guidelines, it was made clear that “cosmetic compatibility tests on human volunteers cannot be considered as a replacement for animal testing,” and that such tests “can only be performed to confirm...that products do not damage skin and mucous membrane, as already expected from other sources.”

There is no explicit legal requirement that the finished products have to be tested in humans at all prior to marketing. There is also no specific regulation on which tests have to be completed prior to testing a cosmetic product clinically in humans. However, it is obvious that the toxicological profile must be available and that there are no concerns based on the data. For instance, if there are, for example, indications for corrosivity of the test product in the nonclinical test model, the product should not be tested in humans to prove the opposite!

Parameters on which data should be available, either based on own tests or derived from literature data (e.g., of known individual ingredients) include:

- Corrosivity
- Mutagenicity
- Genotoxicity
- Carcinogenicity
- Reproductive toxicity
- Dermal/percutaneous absorption
- Phototoxicity
- Acute and repeated dose toxicity
- Sensitizing/photosensitizing potential

1.5 Responsibility Considerations for Planning and Conduct of a Cosmetic Safety Study

Even for clinical testing under a controlled environment, for example, by a Clinical Research Organization (CRO) specialized in these tests, the responsibility for the safety of the test products ultimately remains at the manufacturer. However, for both ethical and liability reasons, the testing organization should always scrutinize all aspects of a planned clinical study to ensure that the health of testing subjects is not harmed due to the study. Even if a specific subject insurance is contracted, which is rarely the case for cosmetic studies since it is not legally required (other than for drug studies), a testing organization may still be liable for compensation of damages to subjects in cases of negligence, which is never covered by this type of insurance. In this respect, the responsible staff of the
testing organization takes a significant part of the responsibility for the safety of the subjects during clinical testing and should therefore always try to minimize the risk for the volunteers to the best of their knowledge.

Often, the manufacturer wants to keep existing data on the test product (e.g., ingredients) confidential, so no complete “picture” of the product is available to the testing organization. However, the testing organization should at least insist on a confirmation by the manufacturer/its safety assessor that the safety assessment and toxicological profile of the test product was considered and the test product is judged safe under the conditions of the study. A formal signed release of the test product stating this must be issued prior to the study. Furthermore, it should be confirmed by the manufacturer that the product conforms to the local (e.g., European) cosmetics laws, for example, by containing ingredients only in the permitted concentrations. It should also be confirmed whether or not the test product contains ingredients never used before in marketed cosmetics. If it does in fact contain a novel ingredient, the testing organization should insist on more information (e.g., a risk assessment by an expert) to be able to take responsibility for the safety of the volunteers during the study.

In general, it should be kept in mind that the list of ingredients in the test product is very helpful for testing. First, to be able to protect test volunteers by excluding them from the study if they already have a known hypersensitivity to a certain cosmetic ingredient which is contained in the test product. Second, an experienced testing organization can consult on the correct choice of the adequate study design to meet the study objectives, which is often critically dependent on the general characteristics of the product, the formulation type, or certain ingredients.

It is not legally required for cosmetic tests that an independent ethics committee reviews the study documents prior to the study. However, this should always be considered, at least if a residual risk for the volunteers is present, for example, if the test product contains novel ingredients, or if invasive or stressful subject procedures are planned for the study. The ethics committees have a perspective “from outside” which can be helpful to detect safety issues.

1.6 Frequent Cosmetic Safety Study Models

Testing cosmetic safety in humans mainly includes investigation of the acute and/or chronic unwanted effects of application of cosmetics on the skin. For this purpose, a variety of safety study models to simulate or even exaggerate the normal conditions of use are employed. Most frequent models are:

- Dermal irritation patch tests, exaggerating normal use. These test models employ controlled single or repeated application of test products to small test fields using special application systems (open, semiocclusively or occlusively). Skin reactions to the test products such as skin reddening (erythema) or scaling are graded by trained observers using standard or modified clinical assessment grading scales.
• In-use irritation tests, simulating normal use. Here the test products are applied repeatedly in an open manner by the subjects. The skin reactions are assessed by trained observers; in addition, biophysical data of the skin (e.g., skin moisture, transepidermal water loss) may be collected. Subjective assessments by the subjects complete the picture.

• Human Repeat Insult Patch Test to assess the sensitization potential of a test product. The product is repeatedly applied during an induction phase, after which follows a rest period and challenge application. Skin assessments for sensitization reactions (allergic potential) are performed following the challenge application. This kind of test is quite controversial. Only very limited information on the long-term consequences for volunteers who have been sensitized during these tests is available. On the other hand, the sample sizes used for this test are often too small to reliably predict a sensitization potential, rendering the study insufficient to meet the study aim.


• At the moment, there is no validated replacement test method available, only a refined animal test (the Local LymphNode Assay). The best approach is apparently choosing ingredients with known low sensitization potential and avoiding those with a known high sensitization potential.

Over the years, the SCCP has also issued several further guidelines/opinions in the area of clinical testing of the safety of cosmetic products.

Weblinks:
http://ec.europa.eu/health/ph_risk/committees/sccp/docshtml/sccp_out45_en.htm

See also the “Guidelines for Assessment of Skin Tolerance of Potentially Irritant Cosmetic Ingredients” issued by COLIPA in 1997.

Weblink:

1.7 Cosmetic Efficacy Testing

In Europe, scientific data substantiating the claims made on the packaging must be available in the product information file (stipulated already in the sixth amendment of the EU cosmetics directive). This data collection may consist of nonclinical (e.g., derived from cell cultures) and/or clinical study data.

In the United States, the situation of cosmetic claim substantiation is quite complicated; however, here also the efficacy claims must be reasonably substantiated to avoid diverse sanctions. The enforcement of claim substantiation standards is shared mainly between the FDA and the FTC (Federal Trade Commission). A good overview of this topic is given by McEwen and Murphy [1].
In Japan, data substantiating efficacy claims is required only for quasi-drugs (i.e., their specific active ingredients) and not for cosmetics. Only specific, authorized claim wording may be used.

The efficacy of cosmetic products may be tested only if there are no founded concerns regarding safety (see section “Cosmetic safety testing”). This is true regardless of the fact that the safety of the product is almost always “cotested” as a secondary objective in a cosmetic efficacy study (e.g., by observing any adverse reactions).

In 2008, the COLIPA issued a revised “Guideline for evaluation of the efficacy of cosmetic products.” This guideline contains general principles for efficacy tests, requirements for test protocols and reports, as well as some sample human and nonhuman efficacy testing models.

Weblink:

Various test designs have been developed in the past years to address the multifaceted requirements of efficacy claim substantiation, driven by marketing interests as well as progress in the understanding of skin physiology. Progress in the field of biophysical measurement and standardized photodocumentation methods provides new opportunities.

In efficacy testing of cosmetics, there are very few test models that are standardized across the industry (one of the exceptions being the International SPF method).

A large number of diverse cosmetic efficacy studies have been published. However, keeping in mind the many possible aspects involved for the diversity of cosmetic products, a cosmetics manufacturer will still need to rely on an experienced cosmetics testing organization to select the adequate study design.

Considering the diversity of the topic, a description of the types of efficacy tests would go too far. However, there is one basic principle to be kept in mind: To deliver relevant substantiation for efficacy claims, the study must simulate normal use.

### 1.8 Cosmetic Labeling and Packaging

The labeling and packaging of cosmetics put on the market is regulated in detail in the respective laws in force in the major markets. For instance, the EU cosmetics directive stipulates that the labeling must contain:

- Name of the marketer
- Weight or volume
- Date of minimum durability (if less than 30 months, otherwise, period of durability after opening)
- Precautions for use
- Batch number
- Product function

Furthermore, in all major markets, the ingredients must be listed using the INCI nomenclature.
In 2006, an international standard for cosmetics packaging and labeling was proposed (ISO 22715:2006). This standard might be adopted internationally in the future. Weblink: http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=36436

An important issue of cosmetic labeling is the efficacy claim which usually appears both on the packaging and advertising material. The claims that are allowed depend on the respective regulatory system (see section above).

A special feature of cosmetics labeling in the USA is that a cosmetic product for which no adequate safety data is available might still be put on the market provided they are labeled “Warning: the safety of this product has not been determined.”

There are no specific regulatory requirements for labeling and packaging of test products for use in a clinical cosmetic study. Apart from common-sense responsibility for the test volunteers, practical aspects are most important here, for example, whether the product is handed out to the volunteers for application at home, storage requirements, blinding, etc. However, the safety of the volunteers should be paramount. The label should include all precaution statements that might be reasonable in the specific setting. Typical labels of test products to be handed out to test volunteers (in-use tests) may include precaution wording such as “for cosmetic study use only,” “keep out of reach of children,” “for external use only,” “store at room temperature in a safe place” etc. Further, brief specific instructions for use may be added on the label. The usage instructions should also be included in an extensive subject information sheet or a treatment diary. Contact information of the investigator may also be added on the label.

References

2. RPA Ltd. for European Commission Directorate General Enterprise: Comparative Study on Cosmetics Legislation in the EU and Other Principal Markets with Special Attention to so-called Borderline Products. Final Report – August 2004
Ethical Aspects of Cosmetic Testing

Hristo Dobrev

Core Message

Cosmetic product safety and claim substantiation have evidently progressed during the past years. A number of skin bioengineering techniques and instrumentation have been developed that are able to prove various cosmetic claims. It is very important that the cosmetic testing on humans is conducted ethically and follow proper scientific design. Compliance with the basic ethical principles originated in the Declaration of Helsinki, and internationally accepted scientific principles of the Good Clinical Practice provides public assurance that the rights, safety, and well-being of participants are protected and that the study data are credible.

2.1 Introduction

Ethical considerations are an essential part of any biomedical research involving human subjects [16, 22].

Medical research is a research conducted to increase the knowledge in the field of medicine. It can be divided into two main categories: basic science (nontherapeutic or nonclinical) medical research and applied (therapeutic or clinical) medical research (clinical trial). The first one predominantly involves healthy persons and is carried out to increase the understanding of fundamental principles and thus to contribute to the applied clinical research. The second one involves sick persons and is intended to evaluate a new diagnostic or therapeutic method for both safety and efficacy.

Studies involving skin measurement methods and testing of cosmetic products on humans are similar to medical research. They involve the use of human beings as research...
subjects and also deal with pure scientific research, whose primary purpose is to contribute to generalized knowledge about the human skin physiology and active substances, and with applied research, aimed to evaluate the safety and efficacy of new cosmetic ingredients and finished products.

In both studies, the ethical considerations are related to the relationship between the physician/the investigator and the human subject/the healthy or sick volunteer and their main objective is the protection of the human being. So, the ethical considerations for cosmetic testing and use of skin measurements are similar to those for medical research on humans, particularly nontherapeutic research. They are subject to the ethical principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice (GCP), and are integrated into the research design.

The aim of this chapter is to outline the ethical aspects of cosmetic testing using non-invasive skin methods.

2.2 Brief History of Research Ethics

Ethics is a set of principles of right human conduct. It deals with moral values such as good or bad, right or wrong, appropriate or inappropriate. Medical ethics is a branch of so-called applied ethics, which explores the application of moral values in medicine. Medical ethics encompasses mainly its practical application in clinical settings and is treated as an applied professional ethics. Research ethics is also a field of applied ethics, which involves the application of fundamental ethical principles to scientific research. It is most developed as a concept in medical research and includes the design and implementation of research involving human experimentation.

Professional medical ethics originates in the Hippocratic Oath written in the fourth century BC by Hippocrates. It is an oath traditionally taken by physicians with which they become obliged to act in conformity with the rules of medical profession and to current best practice for the benefit of the patients. In modern medicine, the significance of the Hippocratic Oath has been reduced to a symbolic right of passage for medical school graduates [23].

The first Code of medical ethics was written by the American Medical Association (AMA) in 1846. It was based upon the guidelines of the English physician Thomas Percival (1740–1804) of Manchester related to physician consultations. This code of ethics dictates the moral authority and independence of professional physicians in service to others and their responsibility towards the sick, as well as the physician’s individual honor [1].

The Nuremberg code (1947) was the first international instrument on the medical research ethics. It was adopted as a consequence of the Nuremberg trial of physicians (the Doctors’ Trial) at the end of the Second World War. The Code was designed to protect the integrity of the research subject and sets out ten conditions for the ethical conduct of research involving human subjects. Among them were such principles as voluntary informed consent, favorable risk–benefit assessment, performance by scientifically qualified persons, termination of the experiment at any stage by subject or scientist either voluntarily or in response to excessive risk, pain, or injury [14, 17, 18].
The Nuremberg code was followed by the Declaration of Geneva and World Medical Association International Code of Medical Ethics. The Declaration of Geneva was adopted by the second General Assembly of the World Medical Association at Geneva in 1948. It was attended as a modern updated revision of the ancient Hippocratic Oath and represents the physicians’ dedication to the humanitarian goals of medicine. The Declaration of Geneva has been revised several times since, most recently in 2006 [27]. The International Code of Medical Ethics was adopted by the third General Assembly of the World Medical Association in London in 1949 and revised in 1968, 1983, and 2006. It indicated the duties of the physicians in general as well as the duties of the physicians to their patients and colleagues [28].

The fundamental document in the field of human research ethics is the Declaration of Helsinki. It was originally adopted at the 1964 World Medical Association General Assembly in Helsinki, Finland, and has undergone six revisions since then (the most recent in October 2008). The Declaration of Helsinki is a comprehensive international statement of the research ethics involving human subjects. It sets out basic ethical guidelines for the medical community regarding the protection of human beings involved in both clinical and nonclinical biomedical research. The first revision of the Declaration of Helsinki (1975) introduced the concept of oversight by an “independent committee” which became a system of Institutional Review Boards (IRBs) in the US, also known as independent ethics committees (IEC) or ethical review boards (ERBs) in other countries, which are empowered to review, approve, and monitor biomedical research involving humans with the aim to protect the rights and welfare of the research subjects. The Declaration of Helsinki was the basis for GCP used today [2, 25, 26, 29].

In 1979, the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research (“The Belmont Report”). It provides guidance for distinguishing therapeutic medicine from research, identifies three fundamental ethical principles for the protection of human subjects (respect for persons, beneficence, and justice), and shows how these ethical principles apply to the conduct of human research (informed consent, assessment of risk and benefits, selection of subjects). These principles continue to provide the ethical foundation for conducting research with human subjects [15, 18].

In 1981, the Department of Health and Human Services (DHHS) issued regulations based on the Belmont Report named Code of Federal Regulation (45 CFR 46). Later, the core of these regulations was formally adopted as “The Federal Policy for the Protection of Human Subjects”, or “Common rule” (1991), which is a rule of medical ethics in the United States [10]. The main elements of the Common Rule include requirements for assuring compliance by research institutions, requirements for researchers obtaining and documenting informed consent, requirements for IRB, additional protections for certain vulnerable research subjects – pregnant women, prisoners, and children [18].

After 1982, the Declaration on Helsinki is not the sole universal guide, since the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) have developed their own biomedical-research ethical guidelines named International Ethical Guidelines for Biomedical Research Involving Human Subjects. The Guidelines relate mainly to ethical justification and scientific validity of
research, ethical review, informed consent, research involving vulnerable individuals, equity regarding burdens and benefits, choice of control in clinical trials, confidentiality, compensation for injury, strengthening of national or local capacity for ethical review, and obligations of sponsors to provide health-care services. The publication was revised/updated in 1993 and 2002. The 2002 CIOMS Guidelines were designed to be of use to countries in defining national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms. ICH guidelines have been adopted as law in several countries, but are only used as guidance for the U.S. Food and Drug Administration [9, 14].

In 1996, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) published its own Guideline on GCP [13]. It was designed to ensure that data generated from the clinical trials are mutually acceptable to regulatory authorities in the European Union, Japan, and the United States of America, as well as those of Australia, Canada, the Nordic countries, and the WHO. GCP guidelines include ethical and scientific standards for the design, conduct, recording, and reporting of clinical research involving the participation of human subjects and define the roles and responsibilities of clinical trial investigators, sponsors, monitors, and research subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, in accordance with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines. It also ensures the integrity of clinical research data. Currently, this guideline is an international quality standard for clinical trials involving human subjects. Any country that adopts this guideline technically follows the same standard.

In 2001, the Council of Ministers of the European Union adopted a Directive on clinical trials (Directive 2001/20/EC) related to the implementation of GCP in the conduct of clinical trials on medicinal products for human use within the European Union [7]. It was intended to simplify and harmonize the administrative provisions governing clinical trials in the European Community, by establishing a clear, transparent procedure. The Articles of the Directive include guidances on protection of clinical trial subjects, ethics committee, conduct of a clinical trial, guidance concerning reports, and many others. The Member States of the European Union were obliged to adopt and publish the laws, regulations, and administrative provisions necessary to comply with this Directive and to apply them from 1 May 2004.

General Medical Council (GMC) in England has also published guidance for Good Practice in Research (Research: The Role and Responsibilities of Doctors) in 2002 [12]. This guidance sets out the general principles and standards expected of all doctors working in research in the National Health Service, universities, and the private sector in England.

In order to assist national regulatory authorities, sponsors, investigators, and ethics committees in implementing GCP for industry-sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research, the WHO issued in 2002, Handbook of Good Clinical Research Practice [24]. The handbook is based on current major international guidelines and is organized as a reference and educational tool to facilitate the understanding and implementation of GCP research process.

At present, regulation of medical research is based on the current international ethical standards as well as on a country’s ethics standard codes.
2.3 Ethical Aspects of Cosmetic Testing

According to EU Cosmetics Directive 76/768/EEC, the cosmetic product must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use. According to the sixth Amendment 93/35/EEC, manufacturer shall for control purposes keep ready information concerned at the assessment of the safety for human health of the ingredients and the finished product as well as proof of the effect claimed for the cosmetic product [5]. In order to achieve these requirements, cosmetic active ingredients and finished products must be tested, including on human volunteers, for evaluation of their safety, compatibility, and efficacy. Studies on cosmetic ingredients and products should be carried out in accordance with the principles of “Declaration of Helsinki” and the guidance for “GCP.” As a rule, safety testing on human volunteers should be preceded by animal or in vitro methods, whereas efficacy testing should be performed when there is evidence that the product does not cause local or systemic adverse responses [11, 19, 20].

Since the past years, there has been a tendency for replacement of animal tests with alternative methods. The seventh Amendment to the Cosmetic Directive establishes a prohibition to test cosmetic ingredients and finished cosmetic products on animals (the testing ban) and a prohibition to market in the EU finished cosmetic products and ingredients included in cosmetic products which were tested on animals (the marketing or sales ban). Both the bans are fully applied from 11 Mar 2009 with the exception of the marketing ban for three types of toxicity tests (repeated-dose toxicity, reproductive toxicity, and toxicokinetics) whose deadline is 11 Mar 2013 [6]. The promotion of scientific and regulatory acceptable alternative methods which reduce, refine, or replace the use of laboratory animals is the main goal of the European Center for the Validation of Alternative Methods (ECVAM) [19].

2.4 Ethical Aspects of Noninvasive Skin Measurements

Due to the developments in bioengineering technology during recent years, it is now possible to evaluate many skin morphology and function parameters by noninvasive instrumental measuring techniques. A “noninvasive” technique means “a procedure or instrument causing minimal and only temporary changes to structure or function, and in particular, not involving pain, incision, or loss of blood” [19]. Skin bioengineering techniques can be successfully applied in safety and efficacy assessment of dermato-cosmetic products to quantify and objectivate the results. They can detect even subtle changes in skin structure and function, and those can enhance the study. Noninvasive skin methods pose no real ethical problems, because they are regarded harmless to the human subject and are not connected with unpleasant or fearful procedures. Since the measurements are only one part of the study, the ethical considerations related to the entire research project are not superfluous. Studies involving noninvasive skin measurements should be conducted according to ethical standards for clinical studies on human subjects [16, 19, 21, 22].
2.5

Essential Ethical Requirements for Performing a Study

Cosmetic testing involving human volunteers must comply with the applicable regulatory requirements for medical research involving human subjects. The basic ethical and scientific principles are provided by the Declaration of Helsinki [25, 26, 29] and current international guidelines for Good Clinical and Research Practices [4, 7, 9, 13, 24] as well as by the guidelines for the evaluation of safety, compatibility, and efficacy of cosmetic products [3, 11], guidelines concerning medical devices [6], and national regulations regarding human studies.

The following principles must be taken into consideration:

2.5.1

Principles Related to Study Conduct

- The study should be preceded by a risk–benefit evaluation, which takes into consideration all study elements (including substances tested and measurement techniques). Concern for the interests of the subject must always prevail over the interests of science and society. The study should be initiated only if the anticipated benefits outweigh the risks.
- The study should conform to a well-designed and scientifically valid methodology according to good practices. The good design would minimize any risks to human beings.
- The design and performance of each procedure should be clearly described in a study protocol, which should be submitted for consideration, comment, guidance, and where appropriate, approval/favorable opinion to an independent institutional review board/Independent ethics committee (IRB/IEC).
- The study should be conducted in accordance with the basic ethical principles, which have their origin in the Declaration of Helsinki.
- The study protocol should always indicate that the ethical principles are observed and an informed consent is obtained.

2.5.2

Principles Related to Study Investigator

- It is the duty of the investigator to protect the life, health, privacy, and dignity of the person on whom biomedical research is being carried out. He must conduct research in an ethical manner and one that accords with the best practice.
- The investigator (research team) should be qualified by education, training, and experience to ensure the proper conduct of the study. He should be thoroughly familiar with the appropriate use of the investigational products and measuring devices as described in the protocol.