Ethical Aspects of Cosmetic Testing

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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

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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 *WMA 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.

- The investigator should inform the participants about all aspects of the study, including its risks and benefits. The information must be written, relevant, understandable, and contain all necessary data to make it possible for human subjects to come to a decision to participate. After ensuring that they have understood the information, the investigator should obtain the subject's freely given competent informed consent which is documented by means of a written, signed, and dated informed consent form.
- The investigator generally assumes responsibility for obtaining IEC/IRB review of the study protocol.
- The investigator should discontinue the research if in his judgment, it may be harmful to the individual, if continued.
- The investigator should ensure adequate compensation and medical services to subjects in case of adverse events or injury related to the study.

2.5.3 Principles Related to Study Subjects/Participants

- The study subjects must be volunteers and informed participants in the research project.
- The study subjects must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, anticipated benefits and potential hazards of the study, and the discomfort it may entail.
- The study subjects should freely give their competent informed consent prior to study participation. They must sign an informed consent document that describes the nature of the study, the products to be tested, known or potential risks, the subject's rights, and whom to contact in case of problems.
- The study subjects should be selected by strict inclusion/exclusion criteria.
- The subjects should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time for any reason without reprisal.
- At the completion of the study, participants are entitled to be informed about the outcome of the study and to share any benefits that result from it.
- The study subjects are eligible to receive appropriate compensation for their time and any inconveniences during the study participation which should be described in detail in the IRB protocol at the time of initial review.
- The study subjects could be secured with adequate insurance provided by the sponsor against claims for any trial-related injuries.

2.5.4 Principles Related to Investigational Products

- Investigational products, i.e., cosmetic products tested should be manufactured, handled, and stored according to the Good Manufacturing Practice of Cosmetic Products (GMPC) and the manufacturing specifications [8]. They should be used only in accordance with the approved study protocol.

2.5.5 Principles Related to Measuring Techniques/Devices

- The skin measuring devices should be manufactured and handled according to the current regulations on medicinal devices. They should bear the CE mark to indicate their conformity with the EU consumer safety, health or environmental requirements [6]. The measuring devices should be used only by or under the control of a suitable qualified professional in accordance with the approved study protocol.

2.5.6 Principles Related to Institutional Review Board/Independent Ethics Committee (IRB/IEC)

- The IRB/IEC is an independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of all human subjects involved in a biomedical research.
- The IRB/IEC should obtain the following documents: study protocol, written informed consent form, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.
- The IRB/IEC should review the scientific merit and ethical acceptability of the proposed study and make a statement in writing within a reasonable time.
- The IRB/IEC should conduct further reviews as necessary in the course of the research and monitor the progress of the study.

2.5.7 Other Considerations

Occasionally, the investigator may consider that it is not essential to obtain an approval for his study from the IRB/IEC. This mainly refers to efficacy cosmetic studies, including the use of skin bioengineering methods. If the tested cosmetic product has been on the market for a long time, it should be considered as safe for human health. If the skin measuring device used is noninvasive, it should be considered as harmless to humans. The initial assessment of whether or not the investigational product and measuring technique represent nonsignificant risk is made by the investigator. However, the final decision should be made by the IRB/IEC. When the proposed research involves no more than minimal risk for human subjects, it could be reviewed by the IRB through an expedited review procedure. The requirement for obtaining informed consent from the study subjects always remains obligatory.

2.6 Conclusion

Ethical principles originating in the Declaration of Helsinki and the generally accepted scientific principles of the GCP should be applied to all biomedical studies involving human subjects. Properly designed and well-conducted cosmetic study supported by skin measuring techniques does not generate particular ethical problems. However, all volunteers should provide signed informed consent, and an approval of the study protocol should be obtained from local ethics committees or other authorized institutions. Compliance with these requirements provides public assurance that the rights, safety, and well-being of the participants are protected and that the trial data are credible.

2.7 Key Messages for Performing an Ethical Study

- A favorable risk/benefit assessment
- Scientific study design
- Voluntary and informed consent
- Strict selection of research subjects
- Ethical approval by IRB/IEC
- Compliance with national and international regulations and standards

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