

Environmental Guidelines No. 10 2000
Vejledning fra Miljøstyrelsen

Guideline on Safety assessment of cosmetic products

Product information/dossier on cosmetic products,
cf. §32 in the Danish Order of Cosmetic Products

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1 Introduction

The purpose of the guideline

The purpose of this guideline is to describe the expectations of the authorities regarding volume and extent of specification of easily accessible information on cosmetic products. At the same time recommendations are given for a practical procedure for collecting and preparing **product information/dossier** covering the individual products. Further, applicable literature is indicated. Thus the guideline should contribute to the effort of preparing uniform cosmetic dossiers at the individual producer.

Jette Rud Larsen, Danish Toxicology Centre, has prepared the present guideline for The Danish Agency of Environmental Protection.

The project has been followed by a steering group, which has contributed with good and constructive advice. The steering group consisted of:

Anette Espersen, The Consumer Council, until the autumn of 1998
Heidi Søsted Rask, The Consumer Council, after the autumn 1998
Liselotte Damgaard, Persano Cosmetics A/S
Henning Gjelstrup Kristensen, The Royal Danish School of Pharmacy
Lars Vælds Frederiksen, A/S Rosco
Søren Ebbeskov, SPT The Association of Danish Cosmetics, Toiletries, Soap, and Detergent Industries
Lisbet Ølgaard, The Danish Agency of Environmental Protection
Lars F. Nørgaard, The Danish Agency of Environmental Protection until the autumn of 1999.

In the spring of 2000 Chapter 2.7 regarding proof of claimed effects was supplemented and a synopsis of the scientific basis is enclosed as Annex 3 to these guidelines. At this time Annette Orloff, The Danish Agency of Environmental Protection became co-ordinator of the guideline.

1.1 Background

Background

Based on the Chemical Substances and Products Act The Danish Agency of Environmental Protection has issued a number of orders with the object of preventing health risks and environmental hazards in connection with production, storage, use and removal of chemical substances and products. One of these statutory orders is the Order of Cosmetic Products (1), which comprises the marketing of cosmetic products. The order has been prepared on the basis of the regulations of the EEC Cosmetics Directive from 1976 incorporating amendments and approximations (2). This guideline describes the requirements of § 32 in the Order of Cosmetic Products, which is based on the requirements of Article 7a in The Cosmetics Directive. This means that corresponding requirements are laid down in the other Member States.

1.2 Legislation

In § 9 of the Order of Cosmetic Products it is stipulated that cosmetic products, which are put on the market within the Community must not cause damage to human health when used under normal conditions.

In substantiation of the safety of the products specific information according to §32 of the Order about all cosmetic products, which are placed on the Community market, must be available. According to the Order of Cosmetic Products the following applies:

§ 32. The manufacturer or his agent or the person to whose order a cosmetic product is manufactured or the person responsible for placing an imported cosmetic product on the Community market shall for control purposes keep the following information readily accessible to the competent authorities of the Member State concerned at the address specified on the label in accordance with § 17.

The required information is mentioned in technical Notes for Guidance from the Scientific Committee for Cosmetic Products and Non-Food Products (SCCNFP) (3). A further description can be found in Chapter 2 of this guideline.

Further, the person responsible for the marketing of a cosmetic product in Denmark must have appropriate professional qualifications or experience in accordance with Danish legislation and common practice.

If the address stated on the product is Danish, The Danish Agency of Environmental Protection is the competent authority, which should make an application to the company in question, whether it concerns control in Denmark or in another Member State. A great amount of the cosmetic products marketed in Denmark carry an address of a company in another Member State. If the Danish Agency of Environmental Protection wants to examine such a product more closely, the Danish Agency of Environmental Protection must make an application to the competent authority in the country of the address stated, and ask the authority to assess the relevant information. Correspondingly, the authorities in other Member States must contact the Danish Agency of Environmental Protection, if they want an assessment of the information in a dossier in this country.

Product information only has to be available in one Member State. Where more company addresses are stated on the label the address where the dossier is kept could be underlined. If the product is manufactured in other Member States, the manufacturer may choose one single address where the information is available. Further, it will be possible that the product information in practice will be available in the head quarters, technical departments, or administrative departments etc., even if these are separated from the actual place of manufacture. If the Danish Agency of Environmental Protection requests that the information is made available, the information must be obtainable at the address mentioned in § 17.

*Sub-contractor
manufacture and
information*

In case of sub-contractor manufacture the name and address of the sub-contractor will not appear from the package. On the contrary, the name and address (country) of the company which ordered the production and which is marketing the product will appear from the package. Thus, a Danish company whose address is stated on a cosmetic product must - whether the product is marketed in Denmark or in another Member State - make sure that any foreign sub-contractor is able to supply product information according to the directives of this guideline.

1.3 Elaboration and submission of information

*Language of information
and confidentiality*

Product information/dossier must be prepared in a language, which is easily understood by the Danish authorities. The Danish Agency of Environmental Protection will accept to receive information in Danish or in English. Consequently, it is important to secure those foreign contractors or sub-contractors are able to submit information in these languages.

As a starting point the Danish Agency of Environmental Protection will demand that the requested information is sent to the Danish Agency of Environmental Protection. It should, however, be emphasised that the Danish Agency of Environmental Protection, will typically not demand an entire dossier on a cosmetic product. It will rather be a matter of specific questions regarding selected parts of the dossier. The information can be delivered either on paper or electronically, and must be available to the Danish Agency of Environmental Protection within 48 hours.

Consequently, it will be the exception to the rule if the Danish Agency of Environmental Protection will pay a visit the company in order to go over the dossier to choose the sections of which they want a copy.

The Danish Agency of Environmental Protection will treat the information confidentially.

Annex 1 to this guideline contains a proposal for a checklist for obtaining information on cosmetics. Further, Annex 2 contains a list of literature with proposals for works of reference suitable for collecting information for the preparation of the general toxicological profile of the ingredients. Annex 3 is a synopsis of the scientific basis for efficacy testing of cosmetic products.

2 Product information/dossier requirements

For all cosmetic products the following information must be accessible:

- Product composition, Chapter 2.1
- Physico-chemical and microbiological specifications, Chapter 2.2
- Method of Manufacture, Chapter 2.3
- Safety assessment of the finished product, Chapter 2.4
- Educational requirements of the safety assessor(s), Chapter 2.5
- Undesirable effects on human health, Chapter 2.6
- Proof of claimed effects, Chapter 2.7

In the following the information required will be described in detail.

2.1 Product composition

According to the Order the following can be stated:

- 1) The qualitative and quantitative composition of the product; in the case of perfume compositions and perfumes, the name and code number of the composition and the identity of the supplier.**

Product composition

The complete product composition must be specified stating the trade name and any other identity (qualitative) of each raw material including an indication of the amount of each raw material stating weight percentage (quantitative).

Examples of ingredients could be

Plasticizers, moisturizing substances, stabilisers, viscosity controlling agents, emulsifiers, colorants, preservatives, flavours / fragrances, etc.

Every single ingredient in a raw material including preservatives in a raw material must be identified, e.g. by the following information:

- INCI-name
- CAS-No.
- Chemical name, (e.g. EINECS or IUPAC names)
- Synonyms (e.g. the designation in CFTA, WHO or the European pharmacopoeia)
- EINECS No./ ELINCS No.
- Gross formula, if possible
- Structural formula, if possible, (e.g. CH₃-CO-CH₃)
- Method of manufacture, origin

When using ingredients of botanical or animal origin (e.g. juice, extract, starch or gelatine) the following information is required (cf. Chapter 2.2.2 page 8):

- Which plant/animal has been used.
- From which part of the plant/animal does the material originate.

For plant extracts, which form part of the finished product exclusively as perfume (essential oils) and for other perfumes and perfumed compositions, which often consist of many different fragrances the information about the composition is limited to the name and code number as well as the identity of the supplier.

Corresponding regulations apply to synthetically produced raw materials for flavours and perfumes. Raw materials for flavours and perfumes often consist of many different fragrances, and mixtures of up to 10 - 300 different substances have been identified. The chemical names of the most concerning fragrances as to health hazards, and of the substances, which form a constituent part of the main ingredients in the flavour/fragrance, should be stated.

2.2 Physico-chemical and microbiological specifications

2.2.1 In general

According to the Order the following information must be supplied:

2) The physico-chemical and microbiological specifications of the raw materials and the finished product and the purity and microbiological control criteria of the cosmetic product.

Analytical specifications

For further identification of the raw materials and the finished product these should be characterised by their analytical specifications. Relevant physico-chemical specifications must be stated for each ingredient as well as for the finished product. Especially, the physico-chemical properties, which have influence on the safety-of-use as a cosmetic product, should be stated. These specifications should among other things form the basis of the assessment, which according to Chapter 2.4 is to be carried out regarding the safety for human health of the finished product.

The specifications and other related control criteria for raw materials as well as for the finished product should be determined according to the type and use of product of which they form part

The specifications must comprise the analysis methodologies used with reference to analysis certificates as well as information about acceptance limits for the tests described.

Provided that samples are available, the Danish Agency of Environmental Protection is entitled to be supplied with these samples, if the Danish Agency of Environmental Protection wants to make an analysis of the individual raw materials.

2.2.2 Physico-chemical specifications of raw materials

Specifications of raw materials

A suitable specification of the raw material can be based on the following:

- Physical characteristics: E.g. state (liquid, solid etc.), density, colour and odour (sharp, sweet etc.) and vapour pressure, melting and boiling point, refractive index, flash point and viscosity.
- Chemical characteristics: E.g. acid-base properties (pH), oxidising properties and solubility.
- water content, if the substance is hygroscopic or degradable in connection with humidity.
- Stability, e.g. stability under influence of light, humidity and temperature .
- The identification of the raw material, determined by e.g. IR, GC/MS, HPLC/MS, HPLC/UV, AAS.

Further, the function of the raw material in the finished product must be stated.

If the raw material is described in a pharmacopoeia, the monograph from this can be used. The Danish Agency of Environmental Protection considers the European, the British, the French, the Japanese, and the American pharmacopoeia suitable in this connection.

Raw materials of botanical and animal origin

In case of raw materials extracted from plants or raw materials, which are part of plants, the following should be stated for further identification:

1. Botanical name and family.
2. Which part of the plant is used.
3. From where does the plant descend geographically.
4. When was the plant reaped and which stage of growth had the plant reached.
5. Treatment with pesticides during growth.
6. Production process, including extraction, distillation or cleaning out.
7. Commercial form: A powder or a solution, and solvent, if any.
8. Characteristic ingredients, e.g. active ingredients (in %), microbiological quality as well as impurities.

Generally, material from plants and parts of plants should be examined for pesticide residues etc., radioactivity, toxic metals, possibly contaminated substances and falsifications. If the raw material contains active ingredients described in a pharmacopoeia the analytical methods stated in the pharmacopoeia should be followed.

Corresponding requirements for identification may be relevant for raw materials extracted from animals. As an example can be mentioned tissue from cattle, sheep and goats where certain forms of tissue are not allowed in cosmetic products due to transmittable mad-cow-decease (TSE), cf. Annex 2 to the Order of Cosmetics.

2.2.3 Criteria for physico-chemical purity of raw materials

Physico-chemical purity of the raw materials

Any known impurity, which might have a toxicological effect, must be stated by name and level of content. It could be content of solvent residues, e.g. benzene in Vaseline, monomer residues in polymer compositions, e.g. acryl amide, nitro amines in alkanolamides, heavy metals, pesticide residues etc.

All impurities arising from the production process of the raw materials, or the breakdown products produced during the stability test must be identified. The identification can be made by means of HPLC, GC, AAS or IR.

2.2.4 Physico-chemical specifications of the finished product

Specifications of the finished product

Relevant specifications of the finished product should be stated including physico-chemical specifications as mentioned under raw materials in order that the ordinary quality of the product can be guaranteed by means of these specifications.

2.2.5 Physico-chemical purity of the finished product

Physico-chemical purity of the finished product

It is the responsibility of the manufacturer that the finished product does not contain other impurities or substantial amounts of the impurities than mentioned in the product specifications, e.g. nitro amines, and that these impurities do not influence the safety of the cosmetic product.

2.2.6 Microbiological control of the raw materials and the finished cosmetic product

Microbiological control of the raw materials

It is important to limit the existence of microorganisms in cosmetic products not only to protect the user from harmful effects but also to secure that the product will keep fresh and will not degrade quickly and be spoiled. Aqueous products, for instance, will often have limited keeping qualities as they are especially sensitive to microbial growth.

Raw materials may contribute considerably to microbial pollution of the product, all dependant on their nature and origin, and the demands on microbial purity must be described in the specifications of the raw materials. Especially water must be tested frequently for growth. As a rule, water, which is not sterilised, should not be stored. It might turn out to be necessary to sterilise the water after a demineralisation in order to obtain a sufficiently pure quality of the water, as microorganisms may often pollute ion exchanger columns.

When setting up criteria for microbial pollution there is a differentiation between the following product categories:

1. Products for children under 3 years, skin products and products intended for eye surroundings and mucous membranes.

2. Other products, e.g. rinse off products.

Acceptable levels

The Danish Agency of Environmental Protection considers the following levels to be acceptable in respect of microbial pollution:

Re 1.)

- less than 10^2 aerobe bacteria and fungi per gram or per millilitre of the raw material or the finished product.

Re 2.)

- less than 10^3 aerobe bacteria and 10^2 fungi per gram or per millilitre of the raw material or the finished product.

Further, the following microorganisms must not be found in cosmetic products:

Staphylococcus aureus

Pseudomonas species

Enterobacteriaceae

Candida albicans

The probability of finding the micro-organisms mentioned is, however, extremely limited under the clean manufacturing conditions which are necessary to observe the requirements of no more than 10^2 bacteria and fungi. Consequently, a test for these may, in general, be omitted, when the above-mentioned requirements have been satisfied.

An appropriate number of samples of at least 1-10 g or 1- 10 ml must be taken for control. The amount of samples and the frequency of the control very much depend on the composition and type of product. The control may also depend on how often the product is manufactured. A guideline for the determination of sampling can be to test the first 3 batches in order to get an impression of normal manufacturing conditions. Based on the experience of these tests, compared with the experience from challenge experiments (cf. below) it is determined whether it is necessary to test all batches, or if test of e.g. every 3, every 5, or every 10 etc. will be a sufficient control.

Procedure for microbiological control

A suitable procedure for microbiological control of finished cosmetic products can be found in the European pharmacopoeia, "Total viable aerobic count", (Ph.Eur. 2.6.12) and "Test for specified micro-organisms" (Ph.Eur. 2.6.13.), (4).

The individual manufacturer can perform the microbiological control of the cosmetic products himself. To perform the control correctly it will among other things require controlled, clean premises, microbiological know-how and equipment. The test for specific bacteria and fungi is more demanding to perform.

Efficacy test of the anti-microbial properties

When developing a new cosmetic product, or when changing existing products it is important to secure that the product has anti-microbial properties in order that the content of bacteria and fungi will not cause damage to the product or the user. This can be done either through the

anti-microbial properties of the ingredients or by adding suitable preservatives.

The efficacy of the anti-microbial properties of the cosmetic products is tested in a challenge test. In this test the product is exposed to a definite amount of micro organisms (10^5 - 10^6 germ/ml). When, at normal use, the user runs the risk of being infected, or there is a risk of deterioration of the product, this test must be performed.

Challenge test

The challenge test is described more closely in “Efficacy of anti-microbial preservation” (Ph.Eur. 5.1.3) (4). This describes which micro organisms should be used in the test as well as the entire procedure for adding micro organisms, sampling and count of micro organisms, which survive within the indicated period. The Technical Guidance Notes from SCCNFP (3) state that the micro organisms to be used in the test must be *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*; however, tests with other micro organisms may in certain instances be necessary.

Acceptance criteria

For cosmetic products it is recommended to follow the acceptance criteria described in U.S.P. (Anti-microbial Preservation - Effectiveness) (5). This implies that the bacteria must be reduced to 0,1% of the initial concentration after 14 days, and that the concentration of bacteria after further 14 days is not increased. As to fungi the concentration after 14 days must not exceed the initial concentration, and must stay on the same level after further 14 days.

The anti-microbial properties for the product are sufficient if a significant decrease or no increase in the number of micro organisms can be observed when the product is tested for the intended storage and use. In this connection it is important also to examine whether the packing of the product protects the contents sufficiently. Further addition of preservatives is not desirable, and addition of a higher dose of preservative must in no way replace the demands for good manufacturing practices.

The challenge test should be repeated if it is doubtful whether the product is sufficiently preserved. It must be emphasised that challenge tests do not replace routinely control.

2.3 Method of manufacture

2.3.1 In general

Method of manufacture

According to the Order of Cosmetics the following outlines have been laid down for the actual manufacture of cosmetic products:

- 3) The method of manufacture complying with the good manufacturing practice ensuring that a cosmetic product manufactured under normal conditions is not dangerous to human health and safety.**

It is recommended to follow the Guideline for Good Manufacturing Practices of Cosmetic Products (GMPC) from the Council of Europe (6). It should be emphasised that in order to be able to meet the rest of the requirements of the dossier it is important to ensure full traceability in the manufacturing process.

The manufacturing method must be described by all relevant stages of the process. A documentation system for all stages in the manufacturing process must be set up with reference to the journal for the production series (batch journal), for the finished product and the batch journals for the raw materials. The description of the manufacturing method must, among other things, comprise:

1. A well-defined manufacturing procedure covering all stages of the production, determined by directions for composition, directions for manufacturing and directions for packaging including the choice of suitable packaging to keep the quality of the product. Any deviation from the directions must be reported.
2. Suitable manufacturing facilities, including the staff and training of the staff; apparatus and manufacturing equipment including cleaning requirements as well as raw materials of good quality.
3. Quality control by means of suitable, well-defined and updated test methods.
4. An effective manufacturing journal which as a minimum must contain the following data for each product:
 - Trade name, internal code number etc.
 - Batch number and date.
 - Reference to specifications and methods of control.
 - The result of control test of the product as well as the initials of the person who carried out the tests.

2.3.2 Sub-contractor manufacture

Sub-contractor manufacture and manufacturing method

In case of sub-contractor manufacture it is important that the specifications of the products are clear and unambiguous, and that the person responsible for marketing ensures that the sub-contractor is living up to the above-mentioned requirements (Chapter 2.3.1) and has the necessary manufacturing facilities, equipment, staff etc. at his disposal. Furthermore, directions, specifications etc. must be available in a language, which can be understood in the country from which the product is placed on the market.

There ought to be a written agreement covering the entire manufacturing process, and the person responsible for the marketing should frequently control whether the wage producer is living up to the defined specifications.

2.4 Safety assessment of the finished product

2.4.1 In general

According to the Order the following assessment regarding hazardous properties of the cosmetic products, if any, applies:

4) Assessment of the safety for human health of the finished product. To that end the manufacturer shall take into consideration the general toxicological profile of the ingredient, its chemical structure and its level of exposure.

Procurement of information

Sufficient information to assess the safety of the finished cosmetic product must be procured. The hazardous effects of the individual substances must be assessed based on the criteria of the harmfulness of the substances specified in the Order of Classification (7). It is the intention that the retrieval in the traditional toxicological literature regarding the ingredients should form sufficient basis of the assessment of the finished product without having to test the finished product on animals or human beings. However, as described below, further tests may in certain cases be necessary.

Detailed guidelines for use have already been laid down for several ingredients in cosmetic products in of Annex 3 to 6 in the Order of Cosmetics. Corresponding annexe can be found the Directive on Cosmetics. The determination of the restrictions for use in the annexe mentioned has been made by the Commission based on assessments of the safe use of the substances in cosmetic products in one of the specified ways. If the ingredients are used in the way specified, the safety assessment of the substance in question can as a rule be made with reference to the fact that the substance has been approved for the purpose in question. If the substance, however, is used for other purposes than those laid down in the Order of Cosmetics, or in other concentrations (which for instance is allowed for certain preservatives), an independent assessment is still necessary.

It should, however, be emphasised that it is always the company which places a cosmetic product on the market which is responsible for the safety of the product, cf. §9 of the Order of Cosmetics. Therefore, when assessing the safety of any new, commonly known information on the properties of a substance should be taken into account, if such information is considered to be of importance to the safety of the product.

A bibliography of works of reference suitable for the preparation of the general toxicological profiles for raw materials can be found in Annex 2.

It is important that the toxicological profiles for the substances are adapted to the technical progress in this field.

2.4.2 The general toxicological profile

The general toxicological profile

The assessment of the toxicological effects of the substances is the first step in the safety assessment. The safety assessment must be based on data on the substances and the test results regarding the properties mentioned below.

There may be instances when it does not appear to be necessary or to be technically possible to provide the information: In such cases scientific justification needs to be given.

1. Acute toxicity.
2. Skin absorption.
3. Skin irritation.
4. Mucous membrane irritation.
5. Skin sensitisation
6. Sub-chronic toxicity.
7. Mutagenicity.
8. Phototoxicity and photomutagenicity (only in case of UV-light absorbing substances).
9. Human data (if available).
10. Toxicokinetics.
11. Teratogenicity, reproduction toxicity, carcinogenicity, and additional genotoxicity.

Tests ought to be conducted by using a substance with the same chemical and physical characteristics as can be found in the finished product. When using a known raw material in a new connection the published data of the raw material must be assessed carefully, as it might have been tested as an ingredient in the type of product of which it usually forms part.

Supplementary information

The safety assessment of the final cosmetic products can generally be made based on the knowledge of the toxicity of the individual ingredients. In special cases supplementary information might, however, be necessary:

- If skin penetration or the irritating effects of the substance are increased because of the fact that the ingredients in the cosmetic product in question have another influence on the substance than the solution used in the previous tests of the substance.
- If a new dangerous substance may develop when mixing the individual ingredients and can be proved in the final cosmetic product.

Test procedures

The information can be obtained from data retrieved by means of internationally recognised test procedures. Data can also be obtained from recognised validated alternative test procedures *in vitro* (in e.g. tissue or cells from living organisms), or, when alternative procedures are not recognised or exist, from *in vivo* tests (in living animals).

It is recommended to use the test procedures stated by the Commission in Council Directive 67/548/EEC incorporating amendments (8), (9), or as described in OECD guidelines (10).

If human clinical observations exist, these should also be assessed. Human data can be retrieved from:

- specific toxicological studies or from studies performed for other regulatory purposes, e.g. for working environment purposes;
- the supplier of the raw materials supplemented by data retrieved from databases or published literature.

Also data from previous consumer surveys may be of value in this connection, just as experience and reports regarding undesirable effects of the product (see Chapter 2.7) must be considered carefully.

2.4.3 The chemical structure of the substance

Chemical structure of the substance

The chemical structure, the properties and structural formula of the substance have been described previously in Chapter 2.1 and 2.2. Further, the degree of purity has been determined. For all relevant impurities the allowed maximum concentration of the impurities should be defined based on toxicological data.

It is the responsibility of the manufacturer that there are no other impurities or major amounts of impurities than those, which are chemically defined or technologically unavoidable, which may influence the safety of the finished product.

2.4.4 Safety assessment

Safety assessment

The safety assessment of a cosmetic product to a considerable extent depends on its route of application. The route of application of the product has an influence on how much of the product - and in this connection - how much of each ingredient can be ingested, inhaled or absorbed through skin and mucous membranes. Further, the amount of each ingredient in the individual product has an influence on the safety assessment.

Risk assessment

Before a safety assessment and a risk assessment of a cosmetic product can be initiated, the degree and route of application must be described thoroughly. This cannot be done generally, but must be done case-by-case, all dependent on the unique composition and use of the individual product. An evaluation of whether the application of a cosmetic product can be considered safe for especially vulnerable groups such as children, must as a principal rule form part of the risk assessment. At least, the following factors in the risk assessment must be considered before weighting the individual ingredients:

- Type of cosmetic product, such as shampoo, sunscreens, toothpaste.
- Method of application, e.g. rub-in, rinse-off or non-rinse-off, spray, brush
- The concentration of each ingredient in the product.
- The amount of the product applied at normal use.
- The frequency of the applications, short-term-/long-term use.
- The total skin area of the body to which the product is applied.
- The type of application area, e.g. mucous membranes, eyelashes, sunburned skin, lips.
- The duration of contact, e.g. in connection with rinse-off products.

- Foreseeable misuse which may increase the exposure.
- Type of consumer, e.g. children, old people, people with sensitive skin.
- Amount, which may enter the body and be absorbed.

Which exposure is relevant in connection with the safety evaluation of each product/substance depends on the toxic effect examined. As to toxic effects such as skin irritation or photo toxicity it will be important to know the exposure of the substances per unit of the skin area, whereas for a systemic toxic effect the exposure per unit of the body weight will be relevant.

The way or ways of exposure (e.g. skin, skin exposed to sunlight, mucous membranes, eyelashes, ingestion or inhalation) must be considered at every risk assessment of the products, or when setting up a test program. Other possible ways of exposure than those for which the product is intended must be considered when assessing the safety of the product, e.g. inhalation of hair spray, ingestion of lipsticks etc. Other possible exposure to problematic substances from other sources than those from the cosmetic product should also form part of the risk assessment.

Further, the use of cosmetic products is dependent on many factors, such as season, fashion, age, habits, income, and novelty value. As many of these factors will change in time it will not be possible to stick to a specific level of exposure for each type of cosmetic product. The safety evaluation should therefore be made individually for the products in question.

Examples of typical amounts of ordinary cosmetic products, which follow the normal degree and route of application, are entered in a technical guideline document from the Commission. The data are from 1981 and 1993 (11).

2.5 Educational requirements of the safety assessor(s)

Educational requirements

According to the Order there are the following educational requirements of the person(s) performing the safety assessment of cosmetic products, cf. Chapter 2.4:

- 5) The name and address of the qualified person or persons responsible for the assessment referred to in No. 4. That person must hold a diploma as defined in Article 1 in Directive 89/48/EEC in the field of pharmacy, toxicology, dermatology, medicine or a similar discipline.**

The directive mentioned refers to the introduction of a general agreement on mutual recognition in the EU of diplomas in qualifying higher education.

It is recommended to enclose an complete curriculum vitae for the person stating education, experience etc.

2.6 Undesirable effects on human health

2.6.1 In general

Undesirable effects

According to the Order, the following data on undesirable effects must be submitted:

6) Existing data on undesirable effects on human health resulting from use of the cosmetic product

2.6.2 Registration

Registration of undesirable effects

Each product must be described by trade name and composition stating the complaints of undesirable effects. The information regarding undesirable effects must include the name and address of the complainant as well as the date of the complaint; the name and address do not have to be submitted to the authorities, but are to be used for the follow-up on the complaint. A description of the undesirable effect must include information about which part of the body was affected, how long after the application of the cosmetic product the undesirable effect arose, and whether the product had been used earlier with or without a similar reaction.

In order to increase the value of the information the age, sex, and, if possible, the state of health of the user should be included. The information about undesirable effects should not be limited only to the information reported by a doctor. Careful report data can be valuable for both the safety assessment of the product and for further development or reformulation of the product.

Further, the manufacturer's reaction and handling of the complaint should be stated. Correcting as well as preventive measures must be described.

Data ought to be kept at least as long as the product is on the market.

2.7 Proof of claimed effects

2.7.1 In general

According to the Order the following data must be accessible:

Proof of the claimed effects

7) Proof of the effect claimed for the cosmetic product where justified by the nature of the effect or product.

It is of special importance to be able to document effects, which may have influence on the health of the consumer of the product. As an example of this can be mentioned the sun protection factor in sunscreens for which it must be documented that the sun protection factor provides the claimed safety. Further, a number of other effects may be of significance to health.

If a cosmetic product is claimed to have a specific effect, which makes the consumer expect quite special results, this must also be documented, even if the effect is of no importance in relation to health.

The claimed effect of a cosmetic product must be proved on the basis of scientifically correct testing. In the following a number of principles for correct testing will be described. Annex 3 to this guideline represents the technical background and gives an analysis of methods and principles of efficacy testing.

The principles used for the evaluation and documentation of the effects and adverse effects of medical and non-medicinal treatment are immediately applicable for cosmetic products.

2.7.2 Principles of retrieval of data

The Danish Environmental Protection Agency expects that documentation of the claimed effect of a cosmetic product is based on scientifically correct testing, and that the measurements made are relevant to the claimed effect.

Further, the claimed effect must be tested on the finished products, identical to the products marketed.

Data retrieved from laboratory tests or from literature, including articles from scientific magazines, on the ingredients, which are expected to have the claimed effect, cannot replace documentation in the form of a correctly performed testing of the effects of the finished product. These data are, however, valuable as background documentation when determining a relevant test and evaluating the test results.

Documentation of the effect of a substance must not be made capital of a claimed effect of the cosmetic product. Neither must such results be modified in the form of e.g. praises, in a way, which gives another impression of the product than that documented/found at the testing of the cosmetic product.

Retrieval and presentation of data

Documentation of the claimed effect must be obtained from the testing of the product on humans. It is important that the claimed effect of the product is not tested until it is secured that the product cannot cause health hazards.

When testing on humans ethical as well as practical principles must be considered, among other things the Helsinki Declaration on protection of human test persons, provisions of the Data Surveillance Authority and guidelines for good clinical practice (GCP). Observance of full GCP is not likely to be obtained when testing cosmetic products; however, it is expected that the principles of GCP be used. Further, the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) has described several fundamental principles and recommendations regarding the use of test persons for the examination of cosmetic products in annex 12 of a technical guidance document for testing of cosmetic products (3).

Today there are several non-invasive instrumental methods, which make it possible to test the effects of products on the skin objectively and without surgical intervention. It is important that the measurements are relevant to the claimed effects of the product. Consumer investigations, and examination of relevant effects performed by skilled personnel may also be applicable methods for testing the effect of the product on humans.

Today a number of *in vitro* test methods can also be used; however, these will only give a rough impression of the effect of the product on humans.

The test report must as a minimum contain a description of:

- Raw materials tested.
- Name, title, qualifications and possibly curriculum vitae of the scientist in charge of the tests.
- Method used for the retrieval of information.
- Criteria for the assessment
- Other conditions for the implementation of the test, e.g. frequency and duration of application, -area, -amount etc.

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1. Order of Cosmetic Products. The Ministry of Environment and Energy, Order No. 594 of 6 June 2000 or subsequent editions.
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10. OECD's Guidelines for the Testing of Chemicals. Organisation for the Economic Cooperation and Development.
11. Technical Guidelines Document in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances, Part I.

Annex 1

Check list for retrieval of information on cosmetics

According to The Ministry of Environment and Energy Order of cosmetic products, § 32

Trade name _____

1. Composition up to 100%

Name of substance/chemical name, CAS-No., INCI-name, EINECS/ELINCS, %-contents and function/description of each ingredient in the cosmetic product

re 1 cf. annex _____
re 2 cf. annex _____
re 3 cf. annex _____
re 4 cf. annex _____
re 5 cf. annex _____
etc.

2. Physico-chemical specifications of the raw materials, content of impurities, if any.

re 1 cf. annex _____
re 2 cf. annex _____
re 3 cf. annex _____
re 4 cf. annex _____
re 5 cf. annex _____
etc.

Physico-chemical specifications of the finished product content of impurities, if any.

cf. annex _____

Microbiological control of raw materials

cf. annex _____

Microbiological control of the finished product

cf. annex _____

3. Manufacturing method

Manufacturing directions, cf. annex _____

Batch journal, cf. annex _____

4. Safety assessment

The toxicological profile of the raw materials:

Ingredients (cf. chapt. 1)

re 1 cf. annex _____

re 2 cf. annex _____

re 3 cf. annex _____

re 4 cf. annex _____

re 5 cf. annex _____

re 6 cf. annex _____

re 7 cf. annex _____

re 8 cf. annex _____

re 9 cf. annex _____

etc.

Typical use of the finished product: (cf. Guideline, Chapter 2-4)

Application method

Application frequency

Safety of the finished product, conclusion:

5. Name, address of the person responsible for the safety assessment:

CV: cf. annex _____

6. Undesirable effects of the finished product:

cf. annex _____

7. Proof of the claimed effect of the finished product:

cf. annex _____

Annex 2

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Richardson, M.L. and Gangolli, S.: The Dictionary of Substances and their Effects. Royal Society of Chemistry 1992-1994.

Fisher, A.A.: Contact Dermatitis, 3.ed. Philadelphia: Lea & Febiger, 1986.

Suitable databases:

MEDLINE (Medical Literature Analysis and Retrieval System (MEDLARS®) on-line)
Producer / publisher:
National Library of Medicine (NLM)
Medlars Management Section
8600 Rockville Pike
Bethesda, MD 20894, USA

MEDLINE corresponds to three print indexes: Index Medicus™, Index to Dental Literature, and International Nursing Index.

TOXLINE (Toxicology Information On-line)
Producer / publisher:
National Library of Medicine (NLM)
Specialized Information Services
8600 Rockville Pike
Bethesda, MD 20894, USA

TOXLINE comprises several individual sub-files supplied by different producers.

RTECS (Registry of Toxic Effects of Chemical Substance)
Producer / publisher:
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for Occupational Safety and Health (NIOSH) of the
Department of Health and Human Services of the United
States of America
4676 Colombia Parkway, Cincinnati
Ohio 45226, USA

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Annex 3

Synopsis prepared by Prof. Jørgen Serup. M.D., Ph.D.
Ingeborgvej 42, DK-2900 Hellerup, Denmark

Synopsis of efficacy testing of cosmetic products

Danish Environmental Protection Agency
Ministry of Environment and Energy

June 28, 2000

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Introduction

Council Directive 93/35/EEC of 14 June 1993 (the Cosmetics Directive) (1), which has been implemented in Denmark, states in Article 7a, 1.g:

The manufacturer or his agent or the person to whose order a cosmetic product is manufactured or the person responsible for placing an imported cosmetic product on the Community market shall for control purposes keep the following information readily accessible to the competent authorities of the Member State concerned at the address specified on the label in accordance with Article 6 (1) (a):

...

g) proof of the effect claimed for the cosmetic product, where justified by the nature of the effect or product.

The Cosmetics Directive defines the nature of the effects of cosmetic products in Article 1, 1:

A “cosmetic product” shall mean any substance or preparation intended to be placed in contact with the various external 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.

Thus, depending on the nature and claimed effect(s) of the product, documentation must be available, organized and presented swiftly to competent authorities upon request to the responsible person or party. To be appreciated fully, the documentation must directly address skin signs and phenomena. Effects may include product-induced changes noticeable during product use, protective effects of the product against various insults or prophylactic effects in which untreated skin suffers damage or spontaneous worsening, whereas treated skin remains unaffected or in a favourable condition.

The European Union and the responsible authorities in Denmark have not yet given any detailed guidance to the cosmetic industry on the principles and methods for proper testing of efficacy of cosmetic products, although the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers recently discussed and finally adopted basic criteria for protocols and human testing of skin compatibility (2,3).

Aim

The aim of this synopsis is to outline principles and standards for efficacy testing of cosmetic products that can be used by both responsible authorities in evaluating products and substantiation and the industry in planning efficacy trials. The standards considered primarily apply to the products that, due to their nature, need justification, but the standards are generic and can be applied to cosmetic products in general.

The synopsis focuses on efficacy and does not address safety issues.

Documentation of biomedical efficacy in perspective

In the history of science, efficacy documentation has passed through phases of hypothetical consideration with deduction to clinical situations, empirical experiments in animals and humans, studies of cases and smaller groups, controlled trials and finally randomized controlled trials, introduced more than 50 years ago and now universally accepted as the gold standard for establishing truth in biomedical research with a clinical objective. Further, according to international consensus, a single randomized controlled trial may not suffice to establish a valid general conclusion, and one or more confirmatory trials at additional centres may be required to establish proof in a larger geographical territory.

Several systems have been described for evaluating quality in research. These are condensed into a concept widely used under the name evidence-based medicine.

According to evidence-based medicine, the validity of trials may be ranked as follows (modified from Eccles et al. (4)):

- 1a) evidence according to meta-analysis and systematic review of a number of randomized controlled trials;
- 1b) evidence according to a minimum of one randomized controlled trial;
- 2a) evidence according to a minimum of one controlled trial with no randomization;
- 2b) evidence according to a directly relevant and valid test method;
- 3) evidence according to a valid test method of indirect relevance, for example descriptive trial(s), correlations with other groups and case-control studies; and
- 4) evidence according to case reports, small series, expert statements and reviews.

The principles of evidence-based medicine are not limited to evaluating therapies, whether medicinal or non-pharmaceutical, but are also applied to diagnostic tests and prognostic and preventive studies and are used to evaluate adverse reactions. The principles of evidence-based medicine

can be directly adopted as a system for evidence-based cosmetic treatment.

The need for systematic reviews in medicine has resulted in the Cochrane Library (<http://www.cochrane.co.uk>), a huge database started in 1992 by scientific reviewers based on the proposal of Professor Archie Cochrane, with updated and systematic reviews primarily on therapies and prophylaxis. Reviews are based exclusively on randomized controlled trials. A Cochrane Skin Group was started in 1997 (<http://www.nottingham.ac.uk/~muzd>).

Thus, the randomized controlled trial is applicable to many disciplines in biomedical research testing intervention in body, mind or the environment, and this gold-standard design is directly applicable to the documentation of cosmetic products as well as the development of pharmaceutical products.

The Declaration of Helsinki and protection of subjects participating in trials

The Declaration of Helsinki, adopted in 1964 by the 18th World Medical Assembly, is an ethical recommendation guiding physicians in biomedical research involving human subjects. It has been amended four times, most recently in October 1996. The aim is to protect the integrity and well-being of a subject in a biomedical study by ensuring proper risk assessment and consideration of ethics by an independent review board. Study participants must be well informed and grant written acceptance: informed consent. The Declaration of Helsinki also addresses critical aspects of research such as the study programme and conduct and the educational needs of the research group.

Denmark adopted these principles in 1992 by adopting the Act on a Scientific-Ethical Committee System and the Treatment of Biomedical Research Projects. Such evaluation is required in every biomedical project that includes humans. In Denmark a system with a number of regional ethics committees and one central committee was established. The nature of a cosmetic product, the claim and the study design may determine whether a study is considered biomedical or not. To assess trials, ethics committees in Denmark need a study protocol, a summary for laypeople, the written information provided to subjects entering the study and an informed consent form. The relevant committee can decide based on informal consultation that the trial is not considered biomedical. Thus, a regional ethics committee must be consulted before any human trial on a cosmetic product is started.

Study data are often stored in electronic registers. The Public Authorities' Registers (Consolidation) Act from 1978 applicable to a broad range of electronic registers states that registers with personal information in

which the integrity of the registrants is at risk must be approved by the Data Surveillance Authority, and the register used must be considered secure. Council Directive 95/46/EC of 24 October 1995 (5), which is not yet fully implemented in Denmark, also instituted such protection. In Denmark, under the present rules and administrative practices, any study registered electronically, or manually, containing personal information must be protected under the auspices of the Data Surveillance Authority after evaluation of the study and the security of the register. Thus, the Agency must approve in writing every systematic study of cosmetic products in Denmark. The Agency requests for the purpose of their assessment a brief description of the trial with emphasis on register and data protection.

The ICH tripartite guideline for good clinical practice

The ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline for good clinical practice (ICH GCP), which was primarily developed to document pharmaceutical products, is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (6). Compliance with this now internationally implemented standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the clinical trial data are credible. The declared objective of the ICH GCP Guideline is to provide a unified standard for the European Union, Japan and the United States as a basis for mutual recognition of clinical data by the regulatory authorities in those three jurisdictions.

The ICH GCP guideline is based on the following general principles.

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, including informed consent and confidentiality covering any record or document.
- Trials should be scientifically sound and described in a clear, detailed protocol, and the anticipated benefits should justify the anticipated risks.
- Trials should be conducted in compliance with a protocol that has received prior approval by an ethics committee.
- A physician or dentist should always be responsible for medical decisions and the medical care given.
- Test personnel should be adequately educated and trained.
- All clinical trial information should be recorded, handled and stored in a way that allows it to be accurately reported, interpreted and verified.

- Investigational products should be manufactured, handled and stored according to good manufacturing practice and used according to the protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

The randomized controlled trial in humans is essential in the ICH GCP. The pharmaceutical industry swiftly adopted ICH GCP during 1997, allocated the necessary resources and established elaborate in-house systems with standard operating procedures, quality assurance and quality control. A major educational effort has been undertaken and resulted in an enthusiastic GCP culture in which things are not underdone. Investigators, project leaders, monitors and quality control officers have refined test practices and helped GCP conduct in several ways. The implementation and maintenance of the guideline has become a continuing process with constant refinements and educational activities.

The GCP guideline is directly applicable to the efficacy testing of cosmetic products.

Ambition level for substantiating the efficacy of cosmetic products

The ICH GCP guideline is directly applicable to trials of cosmetic products on humans. This offers responsible authorities and the product users the highest level of certainty that claims made for cosmetic products hold true. The pharmaceutical industry has demonstrated that GCP systems can be practised to a high degree of sophistication, but establishing and maintaining GCP are costly. The pharmaceutical industry has a long tradition of clinical trials based on various national GCP systems introduced some years ago. This platform was important in the successful introduction of ICH GCP during 1997. The same platform is not present in the cosmetic industry, which additionally may have a different company profile, with few large and numerous small and medium-sized enterprises. Thus, an advanced system such as ICH GCP that ensures the credibility of trials in humans is not yet fully and immediately applicable to cosmetic product efficacy testing. Nevertheless, essential elements can be adopted.

Colipa Guidelines for the evaluation of the efficacy of cosmetic products

Colipa (the European Cosmetic Toiletry and Perfumery Association) represents European manufacturers of cosmetic products. In August 1997, Colipa published *Guidelines for the evaluation of the efficacy of cosmetic products*, with general information and some statements about human testing, instrumental evaluation and non-human models (7). The guidelines list essentials such as the need for a formal protocol, a responsible person, the objective and relevance of the trial, schedule,

statistics and recording and interpreting the results. Nevertheless, the value of the guidelines is restricted by the lack of detailed information and a lack of opinion about the essential elements needed for a trial or documentation to be conclusive. It can only serve as a loose framework to inspire cosmetic scientists. The guidelines accept studies carried out on non-human models and published data on ingredients as documentation of the final product.

The industry probably has a number of in-house standards for efficacy testing in a company context, but such standards, which are likely to be detailed, have typically not reached the public domain. In-house standards may be relevant for authorities in assessing individual products if they are made transparent.

Study objectives and reported endpoints in trials documenting the efficacy of cosmetic products

A logical prerequisite for substantiation of a claim in a trial is that the claim be identical to a defined endpoint in a trial. Studies may have one primary endpoint covering the main claim of the product and a number of secondary endpoints. People use cosmetic products to achieve cutaneous effects that they can see using the naked eye, feel with their fingers or smell. Endpoints assessed by users themselves or a representative panel of observers have first-line relevance. In-use assessment by specially trained evaluators may produce more precise and reproducible information on a smaller sample. Scoring scales and visual analogue scales are typically used in such assessment. Scores and scales must display the full range of expected effects in a reasonably balanced way.

Claims as understood by lay consumers may easily differ from claims worded on package inserts and other written material and defined endpoints in trials, and it must be critically considered that there be no deviation in meaning or appreciation from the trial endpoint to the claim understood by the consumer in real-world situations.

Surrogate endpoints are study objectives that provide indirect evidence about the postulated effect of the product on a user. Surrogates may be quantitative and measurable with very high precision and allow very detailed and reproducible information on a small sample and may therefore be more operable than direct user endpoints. Surrogates may include skin structure and function variables measured with noninvasive instrumental methods, chemical and physical properties, and others. However, the validity of a surrogate endpoint depends entirely on its relevance to the in-use situation under real conditions.

The outcome of in vitro testing and arguments based on product composition clearly represent non-human data distant from real endpoints in a user situation.

Instrumental evaluation of efficacy in humans using noninvasive techniques

Several biophysical and computerized methods for objectively characterizing skin structure and function without invading the skin or interfering with the function measured have been developed in recent decades. The techniques characterize: surface properties such as scaling and dryness, colour and pigmentation (colorimetry), relief and wrinkles (profilometry); skin structures (high frequency ultrasound, confocal microscopy); functions such as blood flow (laser Doppler scanning), surface lipids and sebum production (sebumetry), water evaporation and sweating (evaporimetry); and other parameters. The methods typically measure selected properties dependent on the measuring principle and not overall endpoints as normally appreciated by product users in their self-assessment. Many of the techniques are highly precise and accurate, and significant changes may be demonstrable in a limited number of individuals. Hydration, blood flow, skin elasticity, skin thickness and dermis structure are examples of parameters that can be quantified noninvasively using techniques but only assessed with difficulty clinically. Various methods have been formally validated in published guidelines describing typical variables such as measuring conditions and needs for preconditioning of the test individual, laboratory room conditions, instrumental variation and calibration.

The critical factors in noninvasive techniques are as follows.

- The parameter measured must be relevant to the effect of the product and the claim.
- The laboratory facility must be adequate.
- Staff must be specially educated and trained in the test method and procedure.
- Instruments and measurement must be described in a standard operating procedure, and existing guidelines should be followed.
- The instrument used must be calibrated and stable and remain so during the trial.
- Test subjects must be well informed and adequately preconditioned before measurement.
- The recorded data and samples taken must be properly labelled, handled and processed.

The relevance of the parameter measured, direct or surrogate, is an important issue that requires special argument in a trial. Because of the nature of the techniques, a narrow feature is typically measured under special conditions (such as magnification, amplification or filtering) and with high precision.

When noninvasive techniques are being used to substantiate the final product as a stand-alone test, the researcher and the sponsoring company have a special obligation to argue the relevance of the test relative to the effect, claim and use of the final product and the precision and validity of the instrument and the test procedure actually used in the trial.

Thus, noninvasive techniques may measure endpoints in the documentation of efficacy of final products in trials in humans and even evaluate the endpoint as a stand-alone test if the test can be argued to be relevant and valid in relation to the effect and the product claim. The format of the basic design must be a randomized controlled trial.

The standardization group on noninvasive methods of the European Society of Contact Dermatitis published in the journal *Contact Dermatitis* various formal guidelines on instrumental evaluation of skin: transepidermal water loss, colour and blood flow. The *Handbook of non-invasive methods and the skin* provides detailed information on noninvasive methods used for efficacy documentation (8). An informal group named EEMCO (European Group for Efficacy Measurements on Cosmetics and other Topical Products) including industry representatives published various introductory reviews on measuring techniques such as colorimetry and skin elasticity and a guidance paper on clinical evaluation of dryness, which can be used in validating instrumental methods for measuring skin hydration (9).

Information on raw materials and ingredients in substantiating the efficacy of a final product

The efficacy of a final product may refer to a single ingredient, a number of ingredients acting together, the base as such or the complete product. The physicochemical properties and the purity of ingredients, the supplier and the supplied batch of raw material and the whole manufacturing process are known variables influencing the final product. The efficacy of a final product cannot, in general, be proven directly from the recipe listing individual ingredients for the reasons mentioned above, although efficacy may be predicted and argued with some precision depending on the recipe and the background knowledge. Exceptions may occur when, for example, a chemically well characterized ingredient exerts a known, strong effect and is also evaluated with respect to requirements in a formulation and found uncomplicated to formulate or relatively independent of the vehicle. Essentials such as the relationship between dose and concentration or dose and effect, optimum pH and ingredient stability must be known. Peeling agents, acting as corrosive irritants, may represent such an exception, although efficacy always varies somewhat according to vehicle composition and properties.

Thus, strong arguments are needed to substantiate the efficacy of a final product based on information about the recipe and individual ingredients,

and proof of efficacy of final products should, with exceptions, depend on the outcome of relevant testing in humans with application of the product according to anticipated use.

Minor modifications of formulations for which claims have already been established and efficacy proven are a special issue. Proof of efficacy may be maintained if arguments are presented that the change is unimportant for the efficacy endpoint.

Products manufactured using the same recipe by different companies or the same company in different plants are not automatically biologically equivalent. Chemical and physical characterization of the original product and the copy may suffice for documenting equivalence, and this may be backed up by demonstrating similar penetration of the product or essential ingredients into artificial or human skin. A range of sophisticated techniques are known from skin pharmacology.

Efficacy testing directly in humans remains the ultimate test.

In vitro efficacy models

A number of in vitro efficacy models exist. These models can be useful tools in the research and development of a product, for example for the purposes of selecting the best ingredient among various options, for estimating the relationship between dose and efficacy in the laboratory and for other purposes that lead to a best-fit product candidate that is ready to be tested in humans. Nevertheless, in vitro testing can only provide a rough estimate and only add marginal information about a final product unless the test in a proper document has been validated in relation to the anticipated human in-use situation and deemed suitable for substantiating the efficacy of such a final product with respect to the specified effect.

Thus, in vitro tests are important research tools. Nevertheless, these tools are generally not acceptable in documenting the efficacy of final products unless their validity with regard to user relevance and the claim of the product is documented.

Reference to literature

Reference to literature is important in explaining the background of a product, discussing the findings of a test and determining the validity of a test method. Thus, critical review and reference to literature is an important instrument in the process of substantiating the efficacy of cosmetic products in various ways but in itself never comprises proof replacing a randomized controlled trial. Literature remains indicative. Referenced literature must be in depth and complete and at an academic level, carefully selected on rational grounds and presented in a non-

promotional way with balanced information about advantages and disadvantages.

General principles and conclusion

Any claim that must be verified based on the nature of the product and that can be measured must be documented in a randomized controlled trial in humans who are a representative sample of the anticipated user group.

Trials in humans must be conducted in accordance with the intention and main principles of the ICH harmonized tripartite guideline for good clinical practice, which gives international ethical and scientific quality standards for designing, recording and reporting trials that involve the participation of human subjects, but strict adherence to this guideline is not realistic and therefore not felt mandatory in documenting the efficacy of cosmetic products.

Documentation must be based on testing of the final product identical to the product to be marketed.

Claims must be identical to endpoints measured in trials.

User self-assessment and evaluation of user-relevant effects by panellists or trained observers are gold-standard endpoints in trials. Endpoints representing skin structure and function measured by biophysical methods are also acceptable as endpoints if the methods are validated and demonstrated to be precise and if results are shown to be directly relevant to the claimed effect in users.

Data on raw materials and ingredients in a product, pure laboratory testing and reference to the literature are generally informative but not acceptable for documenting the efficacy of a final cosmetic product.

Documentation must always be scientifically sound and relevant to the claim and the intended use of the product.

The documentation must not make claims or be laid out in such a way that various statements dilute, scatter or modify or deviate in opinion or impression from what was actually documented through experimentation.

Notes on design and critical elements in human testing of the efficacy of cosmetic products

As stated above, the elaborate ICH GCP system for human testing is not considered to be realistic for the cosmetic industry at this time. Elements that may be sought implemented immediately in efficacy testing of cosmetic products are addressed in the following.

Evidence-based documentation of the efficacy of cosmetic products

For cosmetic products, as a general rule, the acceptable rank of evidence should be category 1: a minimum of one well-conducted randomized controlled trial. Category 2a may also be acceptable if proper blinding and randomization cannot be conducted for technical or ethical reasons, for example in the documentation of a peeling agent when visible irritation is closely linked with efficacy. Category 2b is acceptable if the test method actually used is validated and its user relevance documented, including determination of the minimum user-relevant difference.

Ethical testing

The spirit of the Declaration of Helsinki would indicate that written information and informed consent should be standard in cosmetic product testing, although it may not be formally required depending on evaluation of a particular trial by a local review board. In Denmark the Data Surveillance Authority must approve a study. Ethics and testing of cosmetic products were addressed previously in this synopsis.

Sponsor and dossier on efficacy

A sponsoring company, institution or person should be assigned to take the main responsibility, including liability, for test subjects. This sponsor should organize a dossier on efficacy documentation, properly secured and with all relevant trial material readily available. British Standard BS 5454:2000 (10) addresses storage conditions and secure storage of source data and documents.

Who can be accepted as responsible for cosmetic product testing?

Cosmetic products are not medicines and differ formally and by their nature and effect-to-safety ratio from medicinal products, and a researcher with documented relevant education and qualification can therefore take responsibility for a test and a research team. Qualifications can be documented in a curriculum vitae and an educational record. Supervision by a physician is not felt necessary unless a medical problem arises or is likely to arise.

Trial protocol

A detailed trial protocol must be prepared before the trial is conducted and properly dated and signed off by the investigator and the sponsor.

Trial design

A randomized controlled trial in humans is the gold standard to be used whenever applicable, independent of the trial endpoint and the method of recording.

Comparator product

A placebo control should be chosen whenever possible. When efficacy is supposed to be related to a single or a few ingredients that can be omitted in the formulation without changing its physical properties and odour, such a placebo formulation without active ingredient(s) is preferable. Special attention should be focused on the need for similarity between test product and comparator with respect to fragrance and odour, viscosity and colour. It may sometimes be impossible to identify or omit active ingredients. A marketed, neutral product claimed to be a moisturizer or a cream base or an otherwise relevant but inert marketed product similar to the test product with respect to odour, viscosity and colour may be chosen as the comparator. The relevant fragrance may be added to the comparator product, if necessary, to approximate similarity. An experimental formulation may also be used, but this must be formulated as an inert reference without any anticipated endpoint effect, positive or negative, that could invalidate it as a comparator formulation. The lack of difference between investigational and comparator products in physical properties may be documented in the laboratory and confirmed in a pilot study in humans that also addresses odour.

Production of test product

Test products should be produced under quality conditions according to the Council of Europe Guidelines for Good Manufacturing Practice of Cosmetic Products (GMPC) from 1995 (11), ideally after scale up in the production line used for the final production.

Calculation of sample size to estimate the size of the groups needed

The state-of-the-art requirement in trials is a statistical power calculation by a statistician. True differences are overlooked if groups are too small, especially if the expected endpoint difference among groups compared is minor and the variation in the measured endpoint is major. It is in the interest of the sponsor that test groups not be too small and that true effect as a basis for claims not be overlooked. Groups smaller than 20 are not usually considered convincing in substantiating cosmetic products that normally induce minor changes, in contrast to medicinal products used for skin diseases. Depending on the study and products tested, major statistically significant differences obtained in groups smaller than 20 might arouse suspicion that the study suffers from a major bias or imperfection of blinding, for example, related to the selection of test subjects, the cosmetic products applied or the measuring methods.

Selecting test subjects according to defined inclusion and exclusion criteria

Study groups must realistically represent the range of anticipated users of the product with respect to such factors as sex, age and social class. Participants with skin diseases or sun-damaged skin may invalidate the results. Positive (inclusion) and negative (exclusion or non-inclusion) criteria should be defined in the trial protocol.

Quantitative and qualitative endpoints and claims: examples

1. Quantitative endpoints and claims can be measured and must be documented by a relevant method from natural sciences.

Example 1. A product is claimed to increase hair growth. This can be documented by serial standard photographs and blinded scoring by trained evaluators, by trichograms that measure the number of hairs per unit of area, by trichograms with measurement of growth rate or by gravimetric determination of hair growth in a defined area. The user-relevant differences have to be known in advance.

Example 2. A product is claimed to reduce the number and size of wrinkles. This can be documented by the user's and evaluator's scoring or assessment on a visual analogue scale, by serial standard photos and blinded scoring or by a skin surface replica and profilometry using predetermined limits for user relevance. A difference in skin microrelief determined on a skin surface replica under magnification and special lighting is not automatically relevant to the user.

2. Qualitative endpoints and claims may be documented by a relevant method known from psychology, if this is considered relevant for a cosmetic product.

Example 3. A product is claimed to increase sexual attractiveness. This can be tested in a relevant test panel.

Example 4. A product is claimed to make the user feel younger. This can be tested in a relevant group of potential users giving their self-assessment.

Qualitative claims for cosmetic products are common and may be regarded as artistic and therefore not misleading, and special testing may not be felt necessary.

Endpoints and measuring methods

The protocol must define the endpoints to be measured and position them as primary and secondary. The relevance of endpoints must be discussed

and argued. Special consideration is obligatory if the endpoint is a surrogate. Measuring methods may be categorized as follows:

- *User self-assessment.* The user herself or himself evaluates the skin structure and function or the subjective feeling defined in the protocol that is expected to be influenced by the treatment and evaluated according to a scoring scheme or a visual analogue scale.
- *Examination by a panel of evaluators.* Observers with a defined background perform the evaluation as objectively as possible according to a defined system (see above).
- *Instrumental measurement.* A measuring device is used following its validation before the trial according to a standard operating procedure describing measuring conditions and variables. The operator must be educated and trained in the use of the instrument.
- *According to samples.* Samples such as scales and surface biopsies may be taken for additional evaluation according to the protocol.

Statistical methods and blinding

The protocol must outline the method of randomization, data processing and statistical methods to be used for data analysis. The analysed sample must include all treated subjects according to the intention-to-treat principle, and drop-outs should be reported in detail. Coding must be used vigorously as an instrument in blinding the trial .

Unblinding and reporting

The subjects should not be unblinded until the data are checked for completeness and correctness, the database formally locked and the statistical calculation concluded. Finally, the study should be disseminated in a written report with all study data tabulated in an annex to clarify any discrepancy or incorrectness that might be considered in the future. It is crucial for the credibility of a trial that the original results can be inspected and recalculated.

Archiving

The source data, source documents and other relevant documentation are archived. Archiving must be organized and secure (10). It must be possible at any time to verify that the subjects really existed, that the trial really took place etc. and that there is no suspicion of fraud.

Computer validation

The computer software used should be specified and databases and data operations should be validated. The US Food and Drug Administration prepared guidance for industry on this (12).

Study conduct and monitoring

Study conduct can be improved if recorded details are pencilled in case report forms and dated and signed by a responsible person, and if the correctness of recordings is checked by an impartial person: a monitor not directly involved with the recording. It should be ensured that the study complies with the protocol. Notes for the file and protocol amendments must be made if changes are introduced.

Quality assurance, quality control and auditing

The credibility of a study depends on control of the trial by a monitor while it is ongoing and on independent quality control and auditing by quality control inspectors. They must check the formal status of the trial including legal approvals and consent form, the test facility and staffs involved, the investigational and comparator products and other factors. They prepare a written report on compliance and deviations in study conduct related to the protocol, standard operating procedures etc. Auditing must include a check of relevant source data and documents such as case report forms and their archiving. Auditing is also necessary to ensure that procedures for blinding and randomization are not invalidated and that fraud is beyond suspicion.

Adverse events and reactions

Adverse events and reactions should be systematically looked for and registered, and a physician should be contacted if health concern arises.

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Annex: terminology

The terms used in this synopsis originate from scientific use. The terms are arranged alphabetically and explained in the context of documenting the efficacy of cosmetic products.

Adverse event or adverse product reaction

An event is any untoward biomedical occurrence in a subject during a trial; a reaction is an untoward occurrence that is possibly or likely related to the product.

Audit

A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, operating procedures, recommended practices and applicable regulatory requirements.

Bias

A point of view that prevents impartial judgement on issues relating to that point of view. Trials attempt to control this through double blinding. Bias is also any tendency for a value to deviate in one direction from the true value. May be prevented by various techniques, including randomization.

Blinding

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Single-blinded usually refers to the subjects being unaware of the assignment, and double-blinding usually refers to the subjects, investigator, monitor and data analyst being unaware of the assignment.

Case report form

A printed or electronic document designed to record all the information the protocol requires to be reported on each trial subject.

Claim

The product claim is the effect of the final product as written in text on the physical product, any package insert, the package or brochures or other written material prepared to inform the user. Claims may also appear in other media such as advertisements, in the format of images and in electronic versions. There may be a primary claim and a number of secondary claims. Claims may also be multiple with no clear rank order.

Comparator product

A reference treatment in a trial: a placebo, a marketed product or another relevant comparator treatment.

Compliance

Adherence to all trial-related requirements and the applicable regulatory requirements.

Control(s)

A reference test object or treatment (comparator product, placebo or negative control) without effect or with documented action (comparator product, active control or positive control). Control(s) may also refer to reference subject(s) meeting various criteria for inclusion and exclusion in the trial.

Documentation

All records in any form that describe or record the methods, conduct and results of a trial, the factors affecting a trial and the actions taken.

Endpoint

An indicator measured in a subject or biological sample to assess efficacy (or safety or another trial objective). Endpoints may be primary and pivotal or secondary and additional. To support claims, endpoints in trials must be identical to or truly reflect the essence of the claim.

Ethics committee

An independent body (a review board or an institutional, regional, national or supranational committee) comprising scientific professionals and lay members responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a trial and for providing public assurance of that protection.

Fraud

Deliberately exerted actions not described in the study protocol or amendments changing a trial, its data and results in a way serving a personal or partisan interest.

Informed consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigational product

A product with declared composition being tested in a trial.

Investigator or responsible scientist

A person responsible for the conduct of a trial at the trial site. If a trial is conducted by a team of individuals at the trial site, the investigator is the responsible leader of the team.

Monitoring

The act of overseeing the progress of a trial and of ensuring that it is conducted, recorded and reported in accordance with the protocol, operating procedures, described practices for proper conduct of trials and applicable regulatory requirements.

Protocol

A document that describes the objective(s), design, methods, statistical considerations and organization of the trial. The protocol also usually gives the background and rationale for the trial.

Quality assurance

All the planned and systematic actions that are established to ensure that the trial is performed and the data generated, documented (recorded) and reported properly according to described general requirements.

Quality control

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled in a particular trial.

Sample size calculation

A statistical calculation of the number of subjects needed in a specific trial to demonstrate or reject a statistically significant difference between trial objectives, taking into account the precision of the measuring system, the variation of the endpoint and the predefined user-relevant change.

Selection

Inclusion of subjects into and exclusion of subjects from a trial according to a set of criteria defined in a study protocol.

Significance

Means likelihood or importance. May refer to the conclusion of a statistical calculation and be expressed as a probability estimate (*P* value). May also refer to a real in-use situation. A statistically significant difference is not automatically significant to the user.

Source data

All information in original records and certified copies of original records of findings, observations or other activities in a trial necessary to reconstruct and evaluate the trial. Source data are contained in source documents, which are data and records on any medium.

Sponsor

An individual, company, institution or organization that takes responsibility for initiating, managing and/or financing a trial.

Standard operating procedure

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Spilker's classical textbook (13) explains some additional terms and some basic principles of clinical trials.

This synopsis was prepared for the Danish Environmental Protection Agency, Ministry of Environment and Energy (Chemicals Division, Wilders Plads Bygning O, DK-1403 Copenhagen K, Denmark) by Jørgen Serup, M.D., Ph.D., Ingeborgvej 42, DK-2900 Hellerup, Denmark.

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