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Safety

Guidelines for Evaluation of Safety of Functional Cosmetics

Task Force Committee for Evaluation of Safety

1. Introduction

Safety assurances for quasi-drugs and cosmetics pertain not only to the safety of the individual ingredients that the products consist of but also to such aspects as the use of the products and the sites on the body where they are to be applied. In this chapter, we look first at the basic thinking behind ensuring the safety of existing ingredients and new ingredients (hereinafter "functional ingredients") whose efficacy has been evaluated in terms of their anti-aging, whitening, and sunscreen functions by means of guidelines; and second, we discuss additional guidelines for checking the safety of preparations containing functional ingredients.

2. Evaluating the Safety of Functional Ingredients

2–1. New Ingredients

2–1–1. Overview of safety evaluation

When testing the safety of new functional ingredients, the primary goal is to ensure that they are safe when used in cosmetics. In the Guidance for the Safety Evaluation of Cosmetics 2001,[1] the test items of acute toxicity, primary skin irritation, cumulative skin irritation, phototoxicity, the human patch test, eye mucous membrane irritation, contact sensitization, photosensitization, and genetic toxicity (reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronucleus in mice or rats) are all considered to be basic indicators. Also, since the efficacy claims for new functional ingredients will be more definite than those for previous ingredients used in quasi-drugs and cosmetics, in addition to the basic tests mentioned above it will also be necessary to test the specifics of their functions and mechanisms of action (modification of specific enzyme activity). Human usage tests of preparations containing them will also need to be included (Fig. 1).

2–1–2. Testing the safety of new functional ingredients

The safety tests for new functional ingredients are percutaneous absorption, repeated dose toxicity, reproductive and developmental toxicity, and carcinogenicity, as well as metabolism, distribution, and excretion. Percutaneous absorption is evaluated after the fundamental testing of the attributes of a substance as a cosmetic ingredient, and if the ingredient is not absorbed then no further safety testing is required since the functions of the ingredient are manifested at the skin surface. If a functional ingredient is absorbed, it will go into the blood stream and the possibility of it causing systemic toxicity is investigated. In that case, basic testing consists of repeated dose toxicity, reproductive and developmental toxicity, and carcinogenicity, establishing test items in accordance with a toxicity profile, and calculating a margin of safety from the amount of the ingredient in the actual usage and the No Observed Adverse Effect Level (NOAEL) obtained from the above testing in order to carry out a quantitative risk assessment. Percutaneous absorption is not the only attribute evaluated. Depending on the results obtained, metabolism, distribution, and excretion are also studied, and if there should be a metabolite whose safety is of concern, the testing of its safety is considered.

In testing the various aspects of the functions and mechanisms of action, it is necessary to establish an optimum testing system for the effects of the functional ingredient on related constituents of the human body and physiological functions, from both the local and systemic viewpoints.

In drawing up a plan for the above testing, one should refer to OECD (Organisation for Economic Cooperation and Development) guidelines,[2] COLIPA (European Cosmetic, Toiletry and Perfumery Association) guidelines, SCCP (Scientific Committee on Consumer Products) guidelines,[3] and ICH (International Conference on Harmonization) guidelines.[4] However, it is not simply a case of following the test procedures in these guidelines to the letter, and it goes without saying that efforts should be made to es-

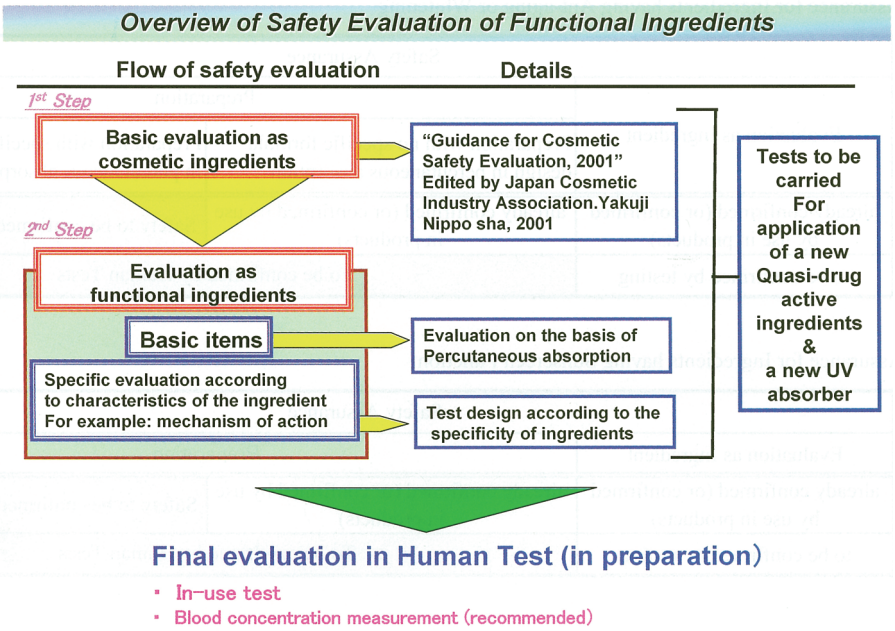

Fig. 1.

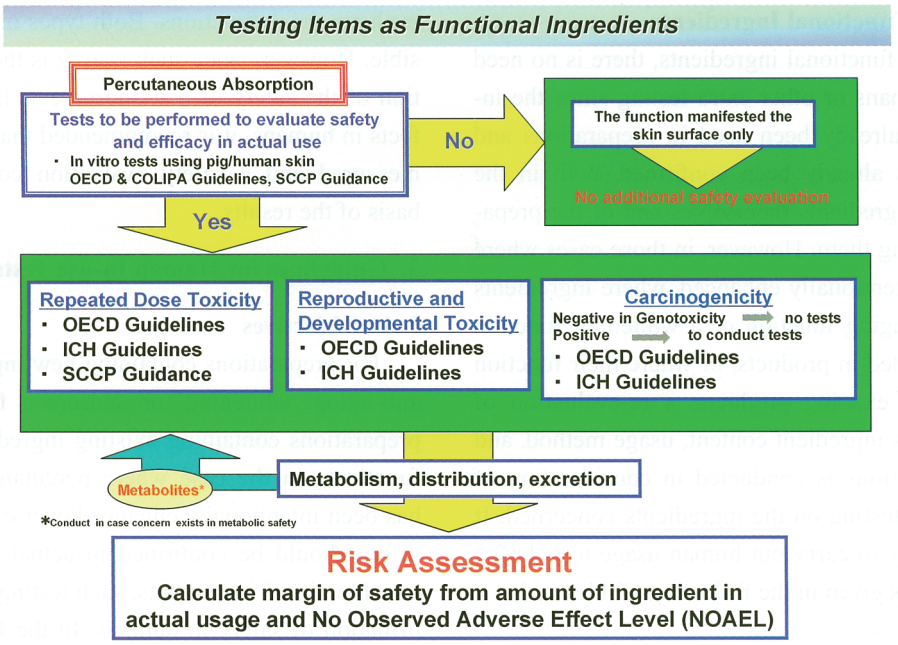

Fig. 2.

tablish optimum testing conditions in consideration of the physical properties of new functional ingredients, past experience with similar ingredients, and the results of preliminary testing (Fig. 2).

For new ingredients having an anti-aging function, a whitening function (active ingredients for quasi-drug products), or a sunscreen function (UV absorbing agent), it is necessary to apply to the Ministry of Health, Labour and Welfare for manufacturing/marketing approval for products containing them or to request their inclusion in a positive list. A checklist of all tests for new ingredients having an anti-aging function or a whitening function may be found in the attachment to Approval Categories for New Quasi-Drugs[1] entitled "Scope of Documentation to Be Included in Approval Dossiers for Quasi-Drugs," which is found in the Cosmetics and Quasi-Drug Manufacturing/Marketing Handbook 2006.[5] In that handbook there is also a comprehensive checklist for new ingredients having sunscreen functions that is entitled "Procedures for Listing

Table 1. Safety Assurance for Ingredients having Ant-aging or Whitening

Type of ingredient	Safety Assurance		
	Evaluation as Ingredient	Preparation	
		Preparation with no specific formula design in percutaneous absorption	Preparation with specific formula design in percutaneous absorption
Approved ingredients	already confirmed (or confirmed by use in products)	already confirmed (or confirmed by use in products)	Safety to be confirmed by Human Tests
New Ingredients	to be confirmed by testing	To be confirmed by Human Tests	

Table 2. Safety Assurance for Ingredients having Sunscreen Function

Type of ingredient	Safety Assurance		
	Evaluation as Ingredient	Preparation	
Approved ingredients	already confirmed (or confirmed by use in products)	already confirmed (or confirmed by use in products)	Safety to be confirmed by Human Tests
New Ingredients	to be confirmed by testing	To be confirmed by Human Tests	

in Positive Lists."

2–2. Existing Functional Ingredients

For existing functional ingredients, there is no need for tests on humans or other extra testing since the ingredients have already been used in preparations and their safety has already been confirmed, both in the testing of the ingredients themselves and of the preparations containing them. However, in those cases where absorption is intentionally enhanced, where ingredients having an anti-aging function or a whitening function are newly included in products, or where their function is enhanced in existing products, a re-evaluation of safety as regards ingredient content, usage method, and application locations is conducted in consideration of previous safety testing on the ingredients concerned. It is then necessary to carry out human usage tests based on the guidelines given in the following (Tables 1, 2).

2–3. Human In-use Tests

For products containing new functional ingredients, those containing existing ingredients having anti-aging or whitening functions, in the case where absorption is intentionally enhanced, such functions are newly included in products, or enhanced in existing products, after conducting the testing in 2–1 above, usage tests on preparations containing the ingredients are conducted according to the guidelines in the following with the purpose of assuring safety when such products are used by humans.

Safety testing can be conducted that involves no evaluation of anti-aging, whitening, or sunscreen functions; and safety testing can be conducted that does evaluate those functions. Both types of testing are possible. However, since such testing is the final confirmation of the safety of new ingredients having strong effects in humans, it is recommended that blood levels be measured and a safety evaluation conducted on the basis of the results.

3. Guidelines for Human In-use Tests

3–1. Objectives

For preparations containing new ingredients having anti-aging, whitening, or sunscreen functions or for preparations containing existing ingredients with these functions, in the case where percutaneous absorption has been intentionally enhanced over existing products, safety should be confirmed in actual usage tests. For new functional ingredients, such testing is the final confirmation of safety in humans. In the following guidelines, only fundamental tests are mentioned, irrespective of the number of subjects, period of application, and types of functional ingredients. Other tests will be the same as those in human testing normally conducted for cosmetics.

3–2. Performance of Testing

As a rule, testing should be conducted by a Japanese Dermatological Association-accredited dermatologist (hereinafter "expert dermatologist"). In actual practice, however, a person with significant experience in safety testing is put in charge, and the testing

may be conducted under the direction of an expert dermatologist if necessary.

3–3. Ethical Guidelines

Ethical considerations should be in accordance with Ethical Guidelines for Clinical Research (Ministry of Health, Labour and Welfare Notification No. 255, 2003), dated 30 July 2003. It is necessary for testing to be approved by an ethics committee and to obtain the informed, written consent of subjects. In order to protect personal information, adequate care must be taken in its filing and management.

3–4. Target Subjects and Exclusion Standards

3–4–1. Subjects

Subjects are healthy persons who understand the purpose of the testing and will cooperate fully in the procedures.

3–4–2. Exclusion standards

(1) Inflammation, rashes, or other skin abnormalities in the test area
(2) General unsuitability in the opinion of the expert dermatologist
(3) In the case of pregnancy or suspected pregnancy, the expert dermatologist will make a decision on whether exclusion is necessary or not.

3–5. Number of Subjects

The number of subjects should be sufficient for demonstrating the novel nature and characteristics of the ingredients and the characteristics of the preparation.

3–6. Application Period and Application Frequency

The application period and application frequency will be set at the minimum levels necessary to demonstrate the novel nature of the ingredient, but the application period must be at least one month. The daily frequency of application during the trial should be the same as that in actual use.

3–7. Test Site

The test site should be the same as the actual site of use.

3–8. Control Sample

To be provided if necessary.

3–9. Evaluation Procedures

(1) When there are two or more groups, the double-blind procedure should be followed.
(2) Questionnaire

Distribute a questionnaire prior to the start of the trial and have it returned after an appropriate period of time. Response items are the following:

•Prior to the start of the trial:
- Cosmetic products normally used
- Current state of skin, skin type, and skin sensitivity
- Any history of skin trouble due to cosmetics, quasi-drugs, or pharmaceuticals
- Presence of allergic constitution, atopic constitution, etc.

•During the trial:
- Daily usage status
- Any skin problems (subjective symptoms, objective symptoms).

(3) Subject examination and interviews

A. Times of examinations and interviews

The times are before starting to use the product and after completion of use. During the period of use, examination times are determined in consideration of the length of the trial.

During the period of the trial, if any of the situations listed below should arise, testing on a subject should be suspended and as far as possible the subject should be examined at the time of suspension in order to evaluate the situation thoroughly. If abnormalities are observed in the area of application, the subject should be followed up until symptoms disappear, and if necessary he or she should be examined by the expert dermatologist:

(i) When a subject wishes to withdraw from the trial
(ii) When continued participation is considered difficult due to adverse events, etc.
(iii) When continued use of the product becomes difficult due to unforeseen events, illness, etc.
(iv) Other situations that an expert dermatologist deems to warrant suspension.

B. Persons conducting examinations and interviews

•Prior to beginning the trial and after completion, an expert dermatologist should conduct the examination and interviews.

•During the period of the trial, an expert dermatologist or trial coordinator should conduct the exami-

nations and interviews.

C. Examination items

•Skin condition

Subjective symptoms: itchiness, irritation, etc.

Objective symptoms: erythema, desquamation, papules, pigmentation, depigmentation, telangiectasia, swelling, etc.

•Other symptoms

References

1) Guidance for Cosmetic Safety Evaluation, 2001. Edited by the Japan Cosmetic Industry Association; Yakuji Nippo, Ltd., 2001.
2) OECD guideline 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 416, 420, 423, 425, 428, 429, 452, 453, 471, 473, 476.
3) The SCCP's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 6th revision, 2006. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_s_04.pdf
4) ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guidelines-Safety. http://www.pmda.go.jp/ich/safety.htm
5) Guide to Quasi-drug and Cosmetic Regulations in Japan, Sixth edition (Japanese version); Yakuji Nippo, Ltd., 2006.