Guideline on Assessment of New Cosmetic Substances

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Table of Contents

Table of Contents

CHAPTER 1: Safety

I. Generals

In principle, safety assessment should be based on review of the following information and risk assessment under consideration of amounts of raw materials used or exposed. The “Guideline for Risk Assessment of cosmetic products” should be consulted. However, if scientifically justified, some information may be omitted with attachment of detailed supporting data.

No.	Test Item
1	Single-dose toxicity test
2	1st skin irritation test
3	Eye irritation test
4	Skin sensitization test
5	Phototoxicity test[Note1] - Photoirritation test - Photosensitization test - Photogenotoxicity test
6	Appropriate toxicity tests, such as repeat-dose toxicity, reproductive toxicity, genotoxicity and carcinogenicity[Note2]
7	Inhalation toxicity test[Note3]
8	Human patch test
9	Skin absorption test

Note 1) This test may be exempted, if absorbance test data is submitted to demonstrate the absence of UV absorption.

Note 2) Limited to preservatives, sunscreens and color additives.

Note 3) Limited to raw materials used in the manufacture of spray products.

II. Study Requirements

1. Tests should be performed in compliance with the Good Laboratory Practice (GLP) Regulation (MFDS Notice).

2. However, human patch test should be performed at domestic or foreign universities or professional research centers under the direction and supervision of medical specialists or those with more than 5-year study experience in research centers, hospitals or other related organizations. Requirements and procedures provided in the "Guideline on Human Studies and Effectiveness Assessment of Cosmetics" should be followed.

III. Study Procedures

1. In principle, procedures described in the "Toxicological Studies of Medicinal Products" (MFDS Notice) should be followed. If procedures are not specified, toxicological study procedures described in Annex should be followed.

2. If alternative study procedures and assessment criteria are scientifically and reasonably justified, they may be used.

[Annex]

Annex 1 Single-dose toxicity test

1. Animal: rat or mouse
2. No. of animals: not less than 5 animals per group
3. Administration route: oral or parenteral
4. Dosing level: Appropriate dose level should be established to investigate toxicity. If any death relating to test material is not observed at dose of ≥ 2,000 mg/kg, it is not necessary to establish dose levels.
5. No. of administration: 1 administration
6. Observation:
   * Toxic symptom's type, severity, occurrence, progress and reversibility should be observed and recorded.
   * Observation should be conducted for 14 days.
   * All animals died during and after observation period should be autopsied and, if necessary, histopathological examinations should be conducted for organs and tissues.

Annex 2 Repeat-dose toxicity test

Refer to the "Guideline on Toxicological Study of Cosmetics (I)".

Annex 3 Phototoxicity test

A. Phototoxicity or photoirritation test

In general, the test method using guinea pigs is used.

1. Animal: Animals specified in the relevant test method should be used.
2. No. of animals: not less than 5 animals per group
3. Groups: In principle, there should be test group (administered with test material) and appropriate control group.
4. Light source: UV-A lamp or a combination of UV-A lamp and UV-B lamp should be used.
5. Method: Appropriate one among those listed in 7 should be used.
6. Assessment: Skin reactions shown by animals should be assessed against each method's assessment criteria.
7. Representative methods are as follows:
   (1) Ison method
   (2) Ljunggren method
   (3) Morikawa method
   (4) Sams method
   (5) Stott method

B. Photosensitization test

In general, the test method using guinea pigs is used.

1. Animal: Animals specified in the relevant test method should be used.
2. No. of animals: not less than 5 animals per group

3. Groups: In principle, there should be test group (administered with test material) and appropriate control group.
4. Light source: UV-A lamp or a combination of UV-A lamp and UV-B lamp should be used.
5. Method: Appropriate one among those listed in 7 should be used. Adjuvant may be used to cause the increased sensitization by test material.
6. Assessment: Skin reactions shown by animals should be assessed against each method's assessment criteria.
7. Representative methods are as follows:
   (1) Adjuvant and Strip method
   (2) Harber method
   (3) Horio method
   (4) Jordan method
   (5) Kochever method
   (6) Maurer method
   (7) Morikawa method
   (8) Vinson method

C. Photogenotoxicity test

Photogenotoxicity test should be performed according to methods described in the following documents.

1) OECD guideline 480
2) OECD guideline 473
3) Photochemical genotoxicity: principles and test methods. Report of GUM task force [Brendler-Schwaab, 2004]

Annex 4 Human patch test

1. No. of human subjects: not less than 30 subjects
2. Application concentration/dose: While considering the raw material's concentration at the time of use, multiple concentrations and doses should be selected for this test.
3. Application site: Appropriate sites, such as upper back (except the median line) and forearm, should be selected for application of patches.
4. Observation: In principle, patches should be removed 24 hours after application and observation and assessment should be conducted after transient red spots arising from removal of patch disappear.
5. Results and assessment: The degree of erythema, edema and others should be assessed by dermatologists or other equivalent persons.

Annex 5 Skin absorption test

Refer to the "Guideline on *in vitro* Skin Absorption Test".

CHAPTER 2: Specifications

I. Generals

1. Specifications should be established in four steps: establishment of test items, establishment of test methods, establishment of acceptance criteria and verification of established specification tests. Acceptance criteria for quality control should be established under consideration of the relevant substance's stability and others. However, when acceptance criteria are established on the basis of in-house test results, means of results obtained from 3 tests per 3 lots ("actual values") may be used.

2. Format, terms, units, symbols and others provided in the "Standards and Test Methods of Functional Cosmeticts" (MFDS Notice) should be followed.

3. In principle, the following items should be included in specifications.

No.	Item	No.	Item
1	Name	9	Rational values
2	Structural or rational formula	10	Purity
3	Molecular formula and molecular weight	11	Loss on drying, loss on ignition or water
4	Origin	12	Residue on ignition
5	Content	13	Other tests
6	Manufacturing method	14	Assay
7	Appearance	15	Reference standards, reagents, test solutions
8	Identification		

Depending on the nature of the substance, unnecessary items may not

be included.

4. Description of test methods: Test methods should be described in detail. However, for general test methods listed in the Korean Pharmacopoeia, compendia in the "Designation of Compendia and Drug Formularies" as determined by the Minister of Food and Drug Safety, and Standards and Test Methods prescribed by the Minister of Food and Drug Safety, all or some information on such test methods may be omitted, provided that the reference information is clearly provided.

II. Description of Each Item

1. Name

In principle, a common name should be described and, if possible, its English name, chemical name, trade name and others should be provided.

2. Structural formula or rational formula

Information on structural formula or rational formula should be provided according to the method described in the Korean Pharmacopoeia.

3. Molecular formula and molecular weight

Information on molecular formula and molecular weight should be provided according to the method described in the Korean Pharmacopoeia.

4. Origin

If it is a synthetic substance of which chemical structure is defined, it is not necessary to provide information on origin. However, for herbal medicines, animal extracts, protein extracts and enzymes, information on their origins should be provided. If it contains more than 2 compounds of similar structures, such as optical isomers, geometric isomers, stereoisomers and high polymers and it is difficult to isolate or purify them or it is not necessary to perform such manipulations, information on

their ratios should be provided.

5. Content

(1) In principle, content should be in the range of 95.0-105.0%. However, if another content range is approved in the country of manufacture or original development or if another range can be justified, the content range may be differently established.

(2) Content should be expressed in percentage (%) and molecular formula should be described in brackets. If it is not appropriate to express content in percentage (%), potency, nitrogen content or other appropriate ones may be used. If there are more than two kinds of substances, content should be specified for each substance, in principle.

(3) For unstable substances, the range should be determined according to their stability.

(4) If it is obviously impossible to establish the content specification, it may not be established. However, the reason should be described in detail.

6. Manufacturing method

For herbal medicines, animal extracts and others, if it is not possible to define content specification and assay method because substances are not unknown, detailed information on manufacturing method (process temperature, extraction time, amounts of raw materials, types and amounts of solvents, yields and others) should be provided.

7. Appearance

Color, shape, odor, taste, solubility and others should be described in detail.

8. Identification

(1) Specific chemical tests based on the substance's chemical structure and characteristics should be described in the order of color reaction, precipitation, degradation, derivatization, UV/Visible/IR spectrums, special reactions, and qualitative cation/anion reactions. Reactions not applicable to identification of the substance may be excluded.

(2) Specific test methods able to distinguish a substance from its related substances of similar structure should be used. For example, identification test based on the same retention time in chromatography is regarded as "not specific". However, if a detector with specificity is used, the test method's specificity may be accepted.

(3) If a substance is in the form of salt, a test method for identification of such salt should be included.

(4) If a substance can be identified by other test methods, it is possible to cite such methods instead of duplicate description.

9. Rational values

(1) Items to show a substance's nature and purity should be

established.

(2) Rational values mean numbers measured by physical/chemical methods, such as saponification value, refractive index, optical rotation, boiling point, specific gravity, acid value, hydroxyl value, alcohol number, ester value, iodine value, melting point, coagulating point, viscosity, pH and absorbance.

10. Purity

(1) Applicable purity attributes should be described in the order of color, odor, taste, solution's condition, pH, acidity or alkalinity, inorganic salt (sulfate, chloride, nitrate), ammonium, heavy metals, metals (such as zinc and iron), arsenic, organic matters, general foreign materials (meaning impurities potentially introduced, remained, generated or added from production process), residues on evaporation, starting materials/intermediates/by-products/degradants which exist as impurities ("related substances"), other impurities (isomers, residual solvents and others) and readily carbonizable substances.

(2) Solution's condition should be established and described if it can be used in assessing the substance's purity.

(3) For inorganic salts, heavy metals and arsenic, applicable ones should be established and described under consideration of manufacturing method, administration method and dose.

(4) For related substances, their limits should be established as mass or percentage (%) relative to the substance. If liquid chromatography or gas chromatography is conducted without use of standards for

related substances, area measurement range, quantitation limit and methods for identification of related substances (such as relative peak retention time) should be described.

(5) If isomers are separated, limits for isomers not intended should be established and described.

(6) For residual solvents, limits should be established for solvents used in production according to officially accepted methods described in compendia or guideline on residual solvents.

11. Loss on drying, loss on ignition or water

The relevant test methods described in General Tests on "Standards and Test Methods for Functional Cosmetic Products" (MFDS Notice) should be followed.

12. Residue on ignition

The residue on ignition test method described in General Tests on "Standards and Test Methods for Functional Cosmetic Products" (MFDS Notice) should be followed.

13. Other tests

In addition to the above test items, others directly relating to quality assessment, safety and efficacy should be established.

14. Assay

Assay is a test method to measure a substance's amount or unit by

physical or chemical method and it should have high accuracy, precision and specificity. However, if limits for impurities are established in purity tests, a test method with lower specificity may be accepted.

15. Reference standards, reagents, test solutions

(1) For reference standards other than those listed in "Standards and Test Methods for Functional Cosmetic Products" (MFDS Notice), specifications appropriate for intended purposes should be established. For reagents and test solutions other than those listed in "Standards and Test Methods for Functional Cosmetic Products" (MFDS Notice), their preparation methods should be described.

(2) If necessary, purification method (if it is difficult to purchase materials other than the relevant substance, including manufacturing method) should be described for reference standards.

(3) For reference standards for quantitation, their contents should be determined by test methods which can measure absolute amount with impurities controlled by purity tests.

(4) Reference standard's content should be not less than 99.0%. If it is not possible to obtain a reference standard of which content is not less than 99.0%, conversion and correction should be made according to the assay method.

CHAPTER 3: Efficacy

I. Types of Information

1 Sunscreen Products

1. Information on origin and development
2. Effectiveness study data (information on UV absorption or dispersion by concentrations and wavelengths)
3. Human study data on protection from UV A or UV B

2 Preservatives

1. Information on origin and development
2. Preservative test data as prescribed in the Korean Pharmacopoeia or compendia in the "Designation of Compendia and Drug Formularies" as determined by the Minister of Food and Drug Safety. However, if alternative methods and assessment criteria are scientifically and reasonably justified, they may be used.

II. Study Requirements

1. Human studies on protection from UV A and UV B should meet requirements for submission of supporting documents to establish the sun protection factor (SPF) and protection grade of UV A (PA), as specified in the "Regulations on the Examination of Functional Cosmeticts" (MFDS Notice).
2. For others, requirements and procedures described in the "Guideline on Human Studies and Effectiveness Assessment of Cosmetics" should be followed.