Cosmetics Evaluation Committee Report

Cosmetics Evaluation Guidelines

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Cosmetics Evaluation Committee

Task Force Committee for Evaluation of Anti-Aging Function

Task Force Committee for Evaluation of Whitening Function

Task Force Committee for Evaluation of Sunscreen Function

Task Force Committee for Evaluation of Safety

<Cosmetics Evaluation Guidelines>

Preface

Publishing Cosmetics Evaluation Guidelines

Shotaro Harada
President, Japanese Cosmetic Science Society

The role of cosmetic science is to ensure that cosmetic products meet the expectations of consumers. Previously, meeting these expectations simply meant ensuring product safety. However, nowadays, it is not an exaggeration to say that consumers also demand far better cosmetic functionality.

As a dermatologist, an administrative committee member, and now the president of the Japanese Cosmetic Science Society (JCSS), I have been involved in cosmetic science for over 40 years. Research and technologies in a variety of industries including the cosmetic industry have advanced surprisingly fast in the past 40 years. The increased public interest in communication and information disclosure seen over this period is indeed a profound social phenomenon. These days consumers in general think they are entitled to have access to high quality products and adequate information about product features.

The advanced features of recently developed cosmetics have gained social recognition. Not only dermatologists but also general consumers now know that cosmetics help users maintain healthy skin, that sunscreen protects the skin against photoaging, and that some other products are effective for preventing and reducing wrinkles and spots that are signs of aging. Cosmetic manufacturers have been using their own standards for evaluation of such advanced features in product development processes; however, no uniform industrial standard has been developed thus far. Evaluation methods need to be scientific, objective, reproducible, and internationally acceptable. This concept formed the background to the development of the evaluation methods proposed by JCSS, an organization where dermatologists, pharmacological researchers, and ex-administrators share their expert knowledge. Enabling consumers to select products from among evidence based cosmetics (EBC) evaluated in accordance with a uniform standard and maintain healthy skin is in line with the national policy of

encouraging individuals to take responsibility for their own health. EBC is, above all, desired by consumers themselves. It is the mission of cosmetic scientists to make sure that consumers know how useful cosmetics are in maintaining healthy skin.

In 2004, JCSS established the Cosmetics Evaluation Committee as a special committee to develop cosmetic evaluation methods and appointed Professor Makoto Kawashima of the Department of Dermatology, Tokyo Women's Medical University as the chairman. After two-and-a-half years of discussion, the Cosmetics Evaluation Committee presented the final report at the 31st JCSS Meeting in June this year. The Guideline for Evaluation of Anti-Wrinkle Products, Guideline for Evaluation of New Whitening Quasi-Drug Products, Guideline for New Efficacy Claims of Sunscreen Products, and Guideline for Evaluation of Safety of Functional Cosmetology are hereby published as cosmetics evaluation guidelines. For the two-and-a-half years, over 50 dermatologists, pharmacological researchers, ex-administrators, and cosmetic researchers intimately involved in the development of cosmetic science and engaged in repeated discussions. At the same time, the preparation of the actual guidelines, including collection of data and relevant literature and conducting questionnaire surveys, was carried out primarily by committee members from the industry. It was the first attempt to share technological know-how among cosmetic manufacturers. The guidelines are the distillation of expert knowledge about cosmetic science. The cosmetic industry, including experts from other fields closer to consumers, will need to take the initiative and establish effective ways of communicating with consumers. As one of its future missions, JCSS will need to update the guidelines in line with international trends. Establishment of the guidelines is merely the first step. Further cooperation among the relevant parties will be vital.

I deeply thank chairman Kawashima and other dermatologists, committee members from the industry, and members of the working groups for their passion and efforts, without which the guidelines would not have been completed in such a short time.

The publication of the guidelines marks the beginning of a new era in which cosmetic science will form a bridge between the "providers" and "receivers" of products.

Preface

Developing Cosmetics Evaluation Guidelines

Makoto Kawashima
Chairman, Cosmetics Evaluation Committee

With the advent of the aging society, consumer demand for prevention of aging signs such as wrinkles and spots has been increasing. Cosmetic R&D, including that into quasi-drugs that help users maintain healthy skin, has been focusing on improving product features that meet the expectations and demands of consumers, and technologies and devices used for evaluation of product efficacy have advanced greatly. While sufficient data on product usefulness are available, methods of evaluating cosmetics vary among manufacturers. The necessity of developing a uniform evaluation standard has been pointed out by consumers as well as the cosmetic industry itself.

In light of such increasing demands, the Japanese Cosmetic Science Society (JCSS) has had repeated discussions about standards for efficacy evaluation, the efficacy of cosmetics and relevant regulations, and evidence-based cosmetics at symposiums and seminars since 2000. In 2003, the JCSS board decided to address the issue of developing objective evaluation methods by establishing the Cosmetics Evaluation Committee under the initiative of President Shotaro Harada. Individual Task Force Committees were subsequently organized by the JCSS member dermatologists, pharmacological researchers, ex-administrators, and cosmetic researchers (Table 1).

On February 14, 2004, members of the Cosmetics Evaluation Committee and its 4 subcommittees; Task Force Committee for Evaluation of Anti-Aging Function, Task Force Committee for Evaluation of Whitening Function, Task Force Committee for Evaluation of Sunscreen Function, and Task Force Committee for Evaluation of Safety; gathered to determine the direction and objectives of committee activities. The Task Force Committees and their working groups subsequently held enthusiastic discussions (Table 2) and presented the interim report at the 30th Society Meeting in 2005 and the final report, including opinions of JCSS members and key persons from the industry concerning the guidelines (proposals), was published in January 2006 and presented at the 31st Society Meeting in June of that year.

Naturally, evaluation guidelines must be scientific, objective, and reproducible. Common concepts for the 4 individual guidelines included the following criteria. First of all, objectivity and homogeneity of testing should basically be ensured by contracting testing to a third-party organization, contracting sample allocation to a third-party organization or maintaining stable testing conditions. Visual and safety evaluations must be conducted by dermatological specialists, general dermatologists or other trained experts (researchers familiar with cosmetics evaluation) with equivalent clinical experience. Instruments used for measurements must be currently available in the market and used internationally for cosmetics evaluation. To further ensure the objectivity of evaluation, auxiliary use of reference materials for image compensation and a skin color chart is recommended.

Individual guidelines are summarized below.

<Guideline for Evaluation of Anti-Wrinkle Products>

The Guideline for Evaluation of Anti-Wrinkle Products includes separate guidelines for cosmetics and quasi-drugs. Product efficacy is to be evaluated by visual and photographic assessment based on photographs showing wrinkle grade standards as well as instrumental measurement of wrinkles. The efficacy of cosmetics is to be determined based on significant differences in reduction of wrinkles between the application group and the non-application group based on visual or photographic assessment or instrumental measurement. The efficacy of quasi-drugs is to be determined based on significant wrinkle reduction between the quasi-drug (containing active ingredients) group and the placebo group using visual or photographic assessment and instrumental measurement in double-blind studies. Study duration should at least be 2 weeks for cosmetics and 2 months for quasi-drugs. Cosmetics subject to the evaluation test shall be products that claim that they “diminish wrinkles caused by dryness,” and quasi-drugs subject to the evaluation test are products that claim to “reduce wrinkles.” Attached references include “Guideline for Wrinkle Photography” for photographic evaluation, “Guideline for Wrinkle Measurement” for instrumental measurement of wrinkles, and “Wrinkle Grade Standard” for measurement of wrinkle grades.

<Guideline for Evaluation of New Whitening Quasi-Drug Products>

According to the guideline, products are to be determined effective if outcomes are significantly different between the quasi-drug (containing active ingredients) group and the placebo group based on visual or photographic assessment and if instrumental measurements are consistent with the visual or photographic assessment in double-blind studies. Study duration should at least be 1 month considering the action mechanisms of whitening products. Quasi-drugs that aim to "gently improve skin pigmentation" shall be subject to the evaluation test. "Guideline for Skin Pigmentation Measurement" is attached as a reference.

<Guideline for New Efficacy Claims of Sunscreen Products>

Unlike the other guidelines, the Guideline for New Efficacy Claims of Sunscreen Products does not provide a specific measurement method. The existing SPF measurement standard and measurement standard for UVA protection are to be used. A study of the literature on ultraviolet protection showed that products with UVA protection and SPF 15 or higher were necessary to prevent photoaging. The effectiveness of sunscreen in preventing photoaging is widely accepted by dermatologists. Establishing a domestic third-party organization to evaluate SPF and UVA measurements needs to be considered to ensure the objectivity of the basis for photoaging prevention.

<Guideline for Evaluation of Safety of Functional Cosmetology>

The purpose of the Guideline for Evaluation of Safety of Functional Cosmetology is to validate product efficacy including wrinkle reduction and prevention and improvement of skin pigmentation that are not encompassed by the current regulations. Since the traditional concept that the effects of cosmetics penetrate only as far as the stratum corneum no longer applies to modern cosmetics, the guideline provides directions on evaluating product safety in humans. Needless to say, the established safety evaluation of product ingredients still needs to be carried out.

As mentioned earlier, the guidelines were prepared through the collective efforts of JCSS members. Establishment and publication of the guidelines would not have been possible without the commitment of over 50 dermatologists, pharmacological researchers,

ex-administrators, and cosmetic researchers. I would particularly like to thank Yoshinari Matsumoto (chairman of the Task Force Committee for Evaluation of Anti-Aging Function), Masami Hanada (chairman of the Task Force Committee for Evaluation of Whitening Function), Isturo Matsuo (chairman of the Task Force Committee for Evaluation of Sunscreen Function), and Masafumi Iijima (chairman of the Task Force Committee for Evaluation of Safety) for undertaking the difficult task of completing the guidelines in such a short period of time.

The guidelines were established as the first step towards a new usefulness evaluation of cosmetic products. Revisions of guidelines based on newly acquired knowledge and ongoing discussions taking international advances into account will be required in the future. Education and training of experts involved in the evaluation tests will be necessary so that these individuals can keep their knowledge and skills up to date. I hope the guidelines will be further improved based on the frank exchange of opinions and cooperation of JCSS members and other parties involved and that they will eventually provide consumers with tangible benefits.

Table 1. List of Cosmetics Evaluation Committee Members

As of November 8, 2006

Cosmetics Evaluation Committee		
Chairman	Makoto Kawashima	Department of Dermatology, Tokyo Women's Medical University Hospital
Member	Yoshinari Matsumoto	Department of Dermatology, Aichi Medical University School of Medicine
Member	Katsumi Hanada	Department of Dermatology, Hirosaki University, School of Medicine
Member	Itsuro Matsuo	Samoncho Dermatological Clinic
Member	Masafumi Iijima	Department of Dermatology, Showa University School of Medicine
Member	Masanori Ando	Faculty of Pharmacy, Musashino University
Member	Yoko Nakamura	Japan Pharmaceutical Information Center
Member	Toshiki Hirai	Japan Pharmacists Education Center

Task Force Committee for Evaluation of Anti-Aging Function		
Chairman	Yoshinari Matsumoto	Department of Dermatology, Aichi Medical University School of Medicine
Member	Makoto Kawashima	Department of Dermatology, Tokyo Women's Medical University Hospital
Member	Shuji Kitagawa	Pharmaceutics, Kobe Pharmaceutical University
Member	Shinsaku Nakagawa	Graduate School of Pharmaceutical Sciences, Osaka University
Member	Chiharu Koide	Research Division, Kose Corporation
Member	Motoji Takahashi	Research Center, Shiseido Co., Ltd.
Member	Shoji Hayashi	Research Division, Kanebo Cosmetics Inc.
Member	Kimihiko Hori	Beauty Center, Skin Care Laboratories, Kao Corporation
Member	Katsuo Matsumoto	Laboratories, Pola Chemical Industries
Working group	Yukiko Ishizuka	Research Division, Kose Corporation
	Motoki Oguri	Research Center, Shiseido Co., Ltd.
	Ai Oba	Laboratories, Pola Chemical Industries
	Yuzo Kawata	Skin Care Laboratories, Kao Corporation
	Koji Matsue	Research Division, Kanebo Cosmetics Inc.

Task Force Committee for Evaluation of Whitening Function		
Chairman	Katsumi Hanada	Department of Dermatology, Hirosaki University, School of Medicine
Member	Hirotsugu Takiwaki	Department of Dermatology, Tokushima University
Member	Hiroshi Tokunaga	Division of Environmental Chemistry, National Institute of Health Sciences
Member	Makiko Fujii	Showa Pharmaceutical University
Member	Oji Ifuku	Research Center, Shiseido Co., Ltd.
Member	Hisao Iwabuchi	Laboratories, Pola Chemical Industries
Member	Hideyo Uchiwa	Research Division, Kanebo Cosmetics Inc.
Member	Tadashi Suzuki	Research Division, Kose Corporation
Member	Kimihiko Hori	Beauty Center, Skin Care Laboratories, Kao Corporation
Working group	Takayuki Katagiri	Laboratories, Pola Chemical Industries
	Chiharu Koide	Research Division, Kose Corporation
	Minoru Sasaki	Research Division, Kanebo Cosmetics Inc.
	Atsushi Nakajima	Skin Care Laboratories, Kao Corporation
	Kazuhisa Maeda	Research Center, Shiseido Co., Ltd.
	Yuki Mizutani	Research Division, Kose Corporation

Task Force Committee for Evaluation of Sunscreen Function		
Chairman	Itsuro Matsuo	Samoncho Dermatological Clinic
Member	Gyo Kawata	Department of Dermatology, Kinki University School of Medicine
Member	Kenji Sugibayashi	Clinical Pharmacokinetics, Department of Pharmaceutical Sciences, Josai University
Member	Seiichi Arai	Beauty Care Laboratories, Toiletries Division, Kanebo
Member	Shin Asano	Research Division, Kose Corporation
Member	Yoshimaru Kumano	Research Center, Shiseido Co., Ltd.
Member	Yuji Suzuki	Skin Care Laboratories, Kao Corporation
Member	Katsuo Matsumoto	Laboratories, Pola Chemical Industries
Working group	Makoto Mizuno	Research Division, Kose Corporation
	Toshio Uesaka	Skin Care Laboratories, Kao Corporation
	Hiroshi Oshima	Laboratories, Pola Chemical Industries
	Masato Hatao	Research Center, Shiseido Co., Ltd.
	Koji Matsue	Research Division, Kanebo Cosmetics Inc.

Task Force Committee for Evaluation of Safety		
Chairman	Masafumi Iijima	Department of Dermatology, Showa University School of Medicine
Member	Atsuyuki Igarashi	Department of Dermatology, Kanto Medical Center, NTT EC
Member	Kunikazu Teshima	School of Nursing & Rehabilitation Sciences, Showa University
Member	Takemi Yoshida	Department of Biochemical Toxicology, School of Pharmaceutical Sciences, Showa University
Double as committee/working group member	Masuo Kato	Research Division, Kanebo Cosmetics Inc.
	Hiroyuki Suzuki	Safety Evaluation Research Center, Kao Corporation
	Yoshiyuki Kawano	Research Center, Shiseido Co., Ltd.
	Takuji Masunaga	Research Division, Kose Corporation
	Fukuyoshi Mori	Laboratories, Pola Chemical Industries
Working group	Yoshiro Hatakeyama	Research Center, Shiseido Co., Ltd.

Secretariat Office	Kazuko Ito	Secretariat Office, Japanese Cosmetic Science Society
	Ikumi Kurimura	LCS

Table 2. Past Committee/Working Group Meetings

Cosmetics Evaluation Committee

February 14, 2004	The 1st review committee meeting/joint meeting
May 10, 2005	The 2nd review committee meeting
June 7, 2006	The 3rd review committee meeting

Task Force Committee for Evaluation of Anti-Aging Function

February 14, 2004	The 1st task force committee
May 10, 2004	The 2nd task force committee
September 2, 2004	The 3rd task force committee
December 2, 2004	The 4th task force committee
April 7, 2005	The 5th task force committee
July 7, 2005	The 6th task force committee
October 6, 2005	The 7th task force committee
March 23, 2006	The 8th task force committee
May 11, 2006	The 9th task force committee

Working Group Meetings

September 21, October 9, and November 17, 2004
January 25, February 24, March 29, May 26, August 8, September 16 and November 18, 2005
March 6, April 21 and August 9, 2006

Task Force Committee for Evaluation of Whitening Function

February 14, 2004	The 1st task force committee
May 7, 2004	The 2nd task force committee
March 24, 2005	The 3rd task force committee
December 2, 2005	The 4th task force committee
April 13, 2006	The 5th task force committee

Working Group Meetings

November 10, December 14 and December 17, 2004
June 20, September 7 and October 17, 2005
March 30, 2006

Task Force Committee for Evaluation of Sunscreen Function

March 10, 2004	The 1st task force committee
January 13, 2005	The 2nd task force committee
September 13, 2005	The 3rd task force committee
May 17, 2006	The 4th task force committee

Working Group Meetings

March 10 and November 9, 2004
July 8, August 31 and November 29, 2005
April 20, 2006

Task Force Committee for Evaluation of Safety

February 14, 2004	The 1st task force committee
April 20, 2005	The 2nd task force committee
August 31, 2004	The 3rd task force committee
September 20, 2005	The 4th task force committee
May 11, 2006	The 5th task force committee

Working Group Meetings

July 13 and August 25, 2004
April 20, July 8 and July 26, 2005
April 19, 2006

<Cosmetics Evaluation Guidelines>

Guideline for Evaluation of Anti-Wrinkle Products

Task Force Committee for Evaluation of Anti-Aging Function*

1. Introduction

Consumer demand for cosmetics that prevent or reduce wrinkles has been high. Unlike the EU, where the category "anti-wrinkle products" exists as a cosmetic classification, or the U.S., where the description "temporary reduction in wrinkles" can be used to indicate cosmetic efficacy, use of efficacy descriptions that include the word "wrinkle" are not permitted in Japan except where a claim for makeup effect is being made.

In the EU, a claim for cosmetic effect/efficacy can be made based on obtained data as long as efficacy data are retained in accordance with Guidelines for the Evaluation of the Efficacy of Cosmetic Products published by the European Cosmetic, Toiletry and Perfumery Association (COLIPA) and can be disclosed or submitted upon the request of the regulatory authorities. An expert working group, the European Group for the Efficacy Measurements on Cosmetics and Other Topical Products (EEMCO) was established in 1994 to ensure smooth data collection by the industry and facilitate the supervision of data collection activities by the regulatory authorities. EEMCO has been conducting scientific reviews on measurements of cosmetic effect/efficacy and regularly publishing the review outcomes in scientific journals. Past EEMCO reports include assessment of skin topography (skin texture including wrinkles)[6] as well as assessment of moisture retention[1], skin color[2], tensile functional properties[3], skin surface pH[4], and transepidermal water loss (TEWL)[5].

As mentioned earlier, the wrinkle-related efficacy of cosmetics or quasi-drugs is not officially recognized in Japan. However, development of cosmetics with wrinkle preventive or reducing effects has become possible due to development of active ingredients and innovation in the area of formulation technologies. Although the regulatory systems among countries may differ, the actual effects on the skin do not differ

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substantially among products in the market. Now that overseas cosmetics can easily be purchased in Japan, wrinkle prevention/reduction should be approved as a cosmetic efficacy claim in order to further promote globalization. Wrinkle preventive/reducing effects need to be proven based on scientific and reliable assessment methods as a prerequisite for obtaining regulatory approval. Cosmetic manufacturers have been conducting wrinkle assessment using their own methods. The Japan Cosmetic Industry Association established an evaluation committee to standardize the wrinkle assessment method in 1998. For over 5 years, the committee discussed the definition of wrinkle, conducted surveys on wrinkle measurements and evaluations, measured wrinkles based on various methods, evaluated the wrinkle reducing effects obtained by the continuous use of cosmetics, prepared wrinkle assessment guidelines, and reported the outcomes in the Journal of the Japanese Cosmetic Science Society[7)-11)]. However, the activities of the committee have since stagnated without much more progress being made.

The Task Force Committee for Evaluation of Anti-Aging Function further pursued the standardization of wrinkle assessment in order to facilitate the granting of regulatory approval by the Ministry of Health, Labour and Welfare for the anti-wrinkle effects of quasi-drugs. Specifically, outcomes of past reviews/discussions were scrutinized, and additional experiments, literature research, and an opinion survey[12)] were conducted to prepare the guideline for evaluation of anti-wrinkle products for the eye area. The guideline not only provides specific measurements methods but also thorough information on selection of study participants, measuring environment, and efficacy assessment criteria. The guideline was created specifically for crow's feet because it is the most common concern among consumers[12)] and the currently available wrinkle assessment methods mainly target crow's feet. Measurement technologies are rapidly advancing so that the measuring methods provided herein will become outdated as time passes. The measuring methods will need to be revised as necessary.

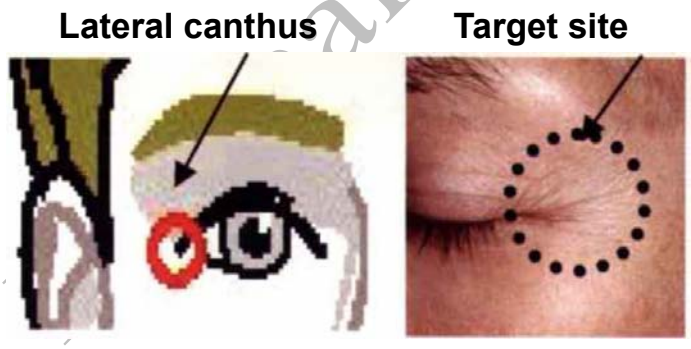
2. Guideline for Evaluation of Anti-Wrinkle Products – Cosmetics

2-1. Target site and study participants

The outer corner of the eye is the target site. Recommended study participants are healthy female or male persons with wrinkles of Grades 1 to 3 (see Fig. 1 Wrinkle Grade Standard) at the outer corner of the eye. Participants are to be randomized to a treatment

group or a non-treatment group by avoiding apparent biases in wrinkle grade distribution, left/right distribution and/or age distribution between the groups. Persons with the same wrinkle grades on left and right should be selected as participants in a study, in which product efficacy is compared between the corresponding sites on left and right in the same person. Target sites are to be randomized to a treatment group and a non-treatment group in a single person. Male-female ratio is to be comparable between the study groups if both sexes are involved. Wrinkles due to disorders are to be excluded. Persons to whom any of the following apply or those who are members of the study center staff are to be excluded.

1) Persons allergic to any cosmetic products
2) Persons receiving hormone replacement therapy
3) Pregnant women and lactating mothers
4) Persons who have undergone any cosmetic procedures that may affect the site to be treated
5) Persons whose participation is otherwise considered inappropriate by the physician



Reference: The outer corner of the eye means the lateral canthus area (where the upper and lower eyelids meet), and crow's feet refer to the linear sulci that runs from the lateral canthus.

2-2. Study centers and environment

Studies are to be conducted under the management of study controllers. In principle, study sponsors are to contract studies to domestic or overseas third-party institutions. However, sponsors may conduct their own studies where "allocation" of samples and application sites and participant recruitment are contracted to third-party institutions. Studies conducted at overseas testing institutions are to include participants

with skin type III or IV (according to Fitzpatrick's classification). Studies are to be conducted in rooms with a controlled environment in which visual assessment, objective instrumental measurements, skin replication, and photographing can be conducted under specific conditions (e.g. temperature, humidity, lighting). When conducting a study at multiple study centers, ensure that measures to avoid inter-institutional errors and inter-observer errors are taken in advance.

2-3. Prohibition

Study participants are to be instructed to avoid undergoing special skin care procedures (e.g. facials) that may affect the skin where test products will be applied within 4 weeks prior to the study and during the study; excessive exposure to ultraviolet radiation such as bathing, mountain climbing, sunbathing, and outdoor exercise; and starting to take new dietary supplements. Use of sunscreens and skin care products are to be avoided or the same products (not including topical products and drugs intended for wrinkle improvement) are to be continuously used during the study.

2-4. Test samples and application

A summary of product features is to be provided for the test sample (e.g. cream, emulsion). The proper amount of test sample is to be applied to the skin during the study until the day before final assessment in accordance with the directions for use (test sample is not to be applied on the assessment day if an interim assessment is scheduled during the study). Test sample information such as composition, manufacturing method, and date of manufacture is to be kept for future follow-up investigation as necessary.

2-5. Duration of study

Studies are to have a duration of at least 2 weeks to ensure that the length of the study period is adequate for evaluation of product efficacy. Studies may be conducted in any season.

2-6. Sample size

Based on preliminary studies, an appropriate sample size for efficacy evaluation is to be calculated. The determined sample size should enable discussion of study outcomes based on statistical data processing.

2-7. Study methods

2-7-1. Test items

- ○ Visual assessment and photographing of the same skin area before test sample application and at the end of the study
- ○ Direct three-dimensional analysis of wrinkles in the same skin area based on instrumental measurements or two- or three-dimensional analysis of skin replicas before test sample application and at the end of the study
  - * Assessments are to be made at several time points before the end of the study as necessary.
  - * Test items necessary for "2-11. Overall efficacy evaluation" are to be selected from among those described above.

2-7-2. Measurement conditions

(1) A room with specific measurement conditions (temperature, humidity, and lighting) is to be used and these conditions are to remain constant throughout the study. Optimum temperature is between 20°C and 22°C, and optimum humidity is 50 ± 5%.

(2) In order to prevent assessment from being affected by makeup, study participants are to wash their faces with the same facial wash before entering the study room and wait for at least 15 minutes until their skin adapts to the environment before starting assessments.

(3) Body posture and position of participants are to be identical in all assessment sessions. Measurement is to be conducted at the same time of day in so far as possible.

2-7-3. Photographing procedure

See "Appendix 1 Guideline for Wrinkle Photography."

2-7-4. Instrumental measurement procedure

See "Appendix 2 Guideline for Wrinkle Measurement."

2-7-5. Endpoints and evaluation method

2-7-5-1. Visual assessment

Visual assessment is to be conducted by dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with cosmetics evaluation) under the supervision of these dermatologists to determine pre- and post-treatment wrinkle grades. Wrinkle grades are to be determined in accordance with the following procedure:

(1) At the beginning of study: baseline score is to be documented based on the wrinkle grade standard photographs (Fig. 1).

(2) Measurement session: At each measuring time point, current wrinkles are to be compared with the photographs taken at baseline or in the previous session to determine the wrinkle grade based on the wrinkle grade standard photographs (Fig. 1).

If none of the standard photographs applies to the current wrinkles, intermediate values or quarter-scores (e.g. 3.5, 3.25) may be used.

2-7-5-2. Photographic evaluation

Dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with cosmetics evaluation) under the supervision of these dermatologists are to score the photographs taken at baseline and each measuring time point based on the wrinkle grade standard photographs (Fig. 1).

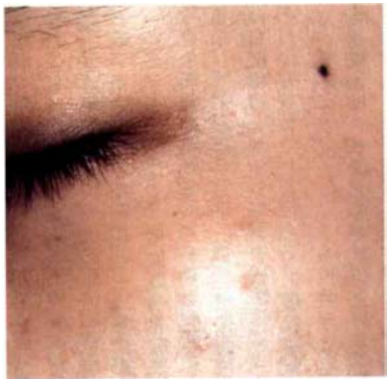
If none of the standard photographs applies to the current wrinkles, intermediate values or quarter-scores (e.g. 3.5, 3.25) may be used.

2-7-5-3. Instrumental evaluation

Wrinkles are to be measured to calculate wrinkle analysis parameters at baseline and each measuring time point using two-dimensional image analysis of skin replicas with oblique lighting, three-dimensional analysis of skin replicas or *in vivo* (direct) three-dimensional analysis.

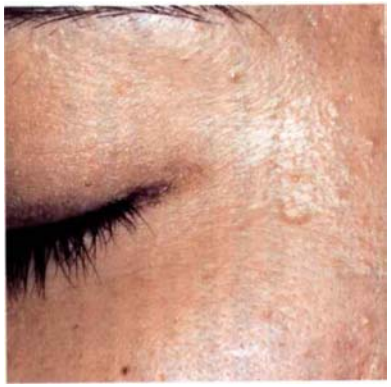
2-8. Participant questionnaire

Participant questionnaire surveys are to be conducted as necessary to monitor problems concerning product use, how the product is used, and product efficacy.



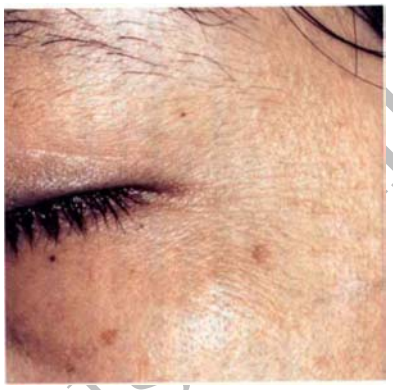
Grade 0

- No wrinkles



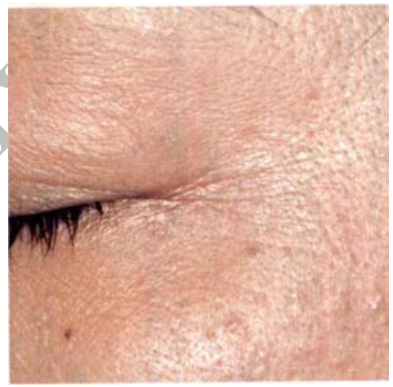
Grade 1

- Undistinguished, shallow wrinkles are seen slightly.



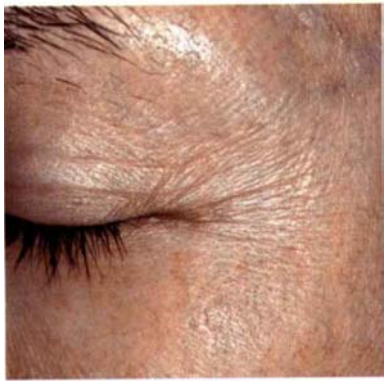
Grade 2

- Distinguished, shallow wrinkles are seen slightly.



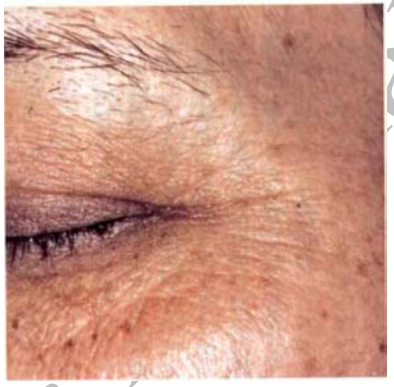
Grade 3

- Distinguished, shallow wrinkles are seen.



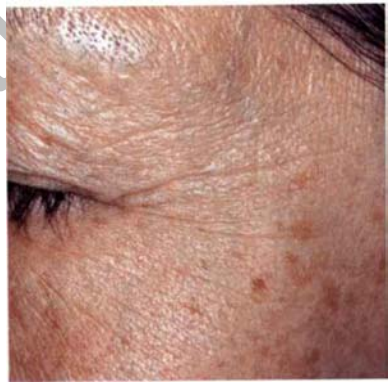
Grade 4

- Somewhat deep wrinkles are seen slightly among distinguished, shallow wrinkles.



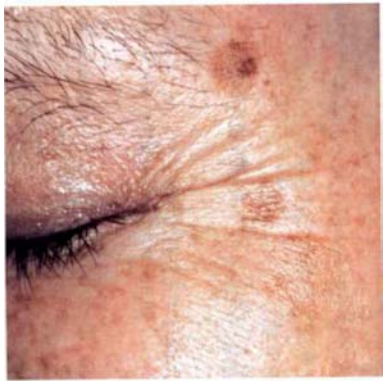
Grade 5

- Somewhat deep wrinkles are seen.



Grade 6

- Distinguished, deep wrinkles are seen.



Grade 7

- Very deep wrinkles are seen.

Fig. 1. Wrinkle Grade Standard

2-9. Adverse events and adverse drug reactions

Adverse events (AEs) mean any and all undesirable events occurring during the trial period, regardless of causal relationships with the test sample. Adverse drug reactions (ADRs) mean undesirable events that occur after using the test sample, in which a causal relationship with the test sample cannot be ruled out.

For any and all AEs and ADRs, details of onset and course, seriousness, treatment given and its details, and prognosis (post-treatment course) are to be documented. Causal relationship with the test sample is to be determined by a physician involved in the study.

2-10. Efficacy analysis

With appropriate statistical analysis methods, changes in all endpoints during the trial period from baseline (before test sample application) to the end of the study in the treatment group are to be compared with those in the non-treatment group. Relevant data should desirably be excluded from the analysis in the event any of the following occur:

(1) Inappropriate product usage such as extremely infrequent use
(2) Occurrence of an AE or an ADR during the trial period that prevents continuation of trial
(3) Compromised data reliability due to use of concomitant drugs, etc.

Product efficacy is to be analyzed in participant groups from which those to whom any of the exclusion criteria above apply have been excluded. Product safety is to be analyzed in all participants who used the test sample.

2-11. Overall efficacy evaluation

Product efficacy is to be determined based on an efficacy analysis that demonstrates significant wrinkle improvement ($p < 0.05$) in visual assessment or photographic evaluation or significant differences ($p < 0.05$) in wrinkle analysis parameter changes in the treatment group compared with the non-treatment group.

2-12. Ethics

Studies are to be conducted in compliance with “Ethical Guidelines for Clinical Research (MHLW Announcement No. 255, 2003)” dated July 30, 2003. Review by and

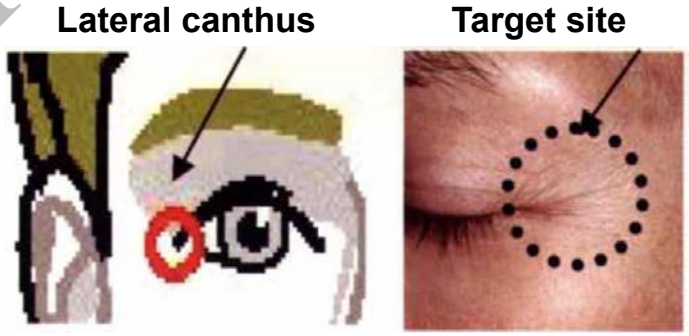
approval of an ethical review board and voluntary written consent of participants are mandatory in any study. The proper storage and management of information is to be implemented to ensure the thorough protection of personal data.

3. Guideline for Evaluation of Anti-Wrinkle Products – Quasi-Drugs

3-1. Target site and study participants

The outer corner of the eye is the target site. Recommended study participants are healthy female or male persons with wrinkles of Grades 1 to 3 (see Fig. 1 Wrinkle Grade Standard) at the outer corner of the eye. An active ingredient group and a placebo group are to be established, and participants are to be randomized to either group by avoiding apparent biases in wrinkle grade distribution, left-right distribution, and age distribution between the groups. In studies in which products are used on corresponding areas on the left and right of the face, participants with comparable wrinkle grades on the left and right of the face are to be included. One side of the face is to be randomized to the active ingredient group and the other side to the placebo group. Male-female ratios in the two groups are to be comparable if both sexes are involved. Wrinkles caused by disorders are to be excluded. Participants to whom any of the following applies are to be excluded.

1) Persons allergic to any cosmetic products
2) Persons receiving hormone replacement therapy
3) Pregnant women and lactating mothers
4) Persons who have undergone any cosmetic procedures that may affect the site to be treated
5) Persons whose participation is otherwise considered inappropriate by the physician



Reference: The outer corner of the eye means the lateral canthus area (where the upper and lower eyelids meet), and crow's feet refer to the linear sulci that runs from the lateral canthus.

3-2. Study centers and environment

Studies are to be conducted under the management of a controller using the double blind method. In principle, study sponsors are to contract studies to domestic or overseas third-party institutions. However, sponsors may conduct their own studies provided "allocations" of samples and application sites are contracted to third-party institutions. Studies conducted at overseas testing institutions are to include participants with skin type III or IV (according to Fitzpatrick's classification). Studies are to be conducted in rooms with a controlled environment in which visual assessment, objective instrumental measurements, skin replication, and photographing can be conducted under specific conditions (e.g. temperature, humidity, lighting). When conducting a study at multiple study centers, ensure that measures to avoid inter-institutional errors and inter-observer errors are taken in advance.

3-3. Prohibition

Study participants are to be instructed to avoid undergoing special skin care procedures (e.g. facials) that may affect the skin where test products will be applied within 4 weeks prior to the study and during the study; excessive exposure to ultraviolet radiation such as bathing, mountain climbing, sunbathing, and outdoor exercise; and starting to take new dietary supplements. Use of sunscreens and skin care products are to be avoided or the same products (not including topical products and drugs intended for wrinkle improvement) are to be continuously used during the study.

3-4. Test samples and application

A summary of product features is to be provided for the test sample (e.g. cream, emulsion). The proper amount of test sample is to be applied to the skin during the study until the day before final assessment in accordance with the directions for use (test sample is not to be applied on the assessment day if an interim assessment is scheduled during the study). Test sample information such as composition, manufacturing method, and date of manufacture is to be kept for future follow-up investigation as necessary.

3-5. Duration of study

Studies are to have a duration of at least 2 months to ensure that the length of the

study period is adequate for evaluation of product efficacy. Studies may be conducted in any season.

3-6. Sample size

Based on preliminary studies, an appropriate sample size for efficacy evaluation is to be calculated. The determined sample size should enable discussion of study outcomes based on statistical data processing.

3-7. Study methods

3-7-1. Test items

- ○ Visual assessment and photographing of the same skin area before test sample application and at the end of the study
- ○ Direct three-dimensional analysis of wrinkles in the same skin area based on instrumental measurements or two- or three-dimensional analysis of skin replicas before test sample application and at the end of the study
  - * Assessments are to be made at several time points before the end of the study as necessary.
  - * Test items necessary for "3-11. Overall efficacy evaluation" are to be selected from among those described above.

3-7-2. Measurement conditions

(1) A room with specific measurement conditions (temperature, humidity, and lighting) is to be used and these conditions are to remain constant throughout the study. Optimum temperature is between 20°C and 22°C, and optimum humidity is 50 ± 5%.

(2) In order to prevent assessment from being affected by makeup, study participants are to wash their faces with the same facial wash before entering the study room and wait for at least 15 minutes until their skin adapts to the environment before starting assessments.

(3) Body posture and position of participants are to be identical in all assessment sessions. Measurement is to be conducted at the same time of day in so far as possible.

3-7-3. Photographing procedure

See “Appendix 1 Guideline for Wrinkle Photography.”

3-7-4. Instrumental measurement procedure

See “Appendix 2 Guideline for Wrinkle Measurement.”

3-7-5. Endpoints and evaluation method

3-7-5-1. Visual assessment

Visual assessment is to be conducted by dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with cosmetics evaluation) under the supervision of these dermatologists to determine pre- and post-treatment wrinkle grades. Wrinkle grades are to be determined in accordance with the following procedure:

(1) At the beginning of study: baseline score is to be documented based on the wrinkle grade standard photographs (Fig. 1).

(2) Measurement session: At each measuring time point, current wrinkles are to be compared with the photographs taken at baseline or in the previous session to determine the wrinkle grade based on the wrinkle grade standard photographs (Fig. 1).

If none of the standard photographs applies to the current wrinkles, intermediate values or quarter-scores (e.g. 3.5, 3.25) may be used.

3-7-5-2. Photographic evaluation

Dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with cosmetics evaluation) under the supervision of these dermatologists are to score the photographs taken at baseline and each measuring time point based on the wrinkle grade standard photographs (Fig. 1).

If none of the standard photographs applies to the current wrinkles, intermediate values or quarter-scores (e.g. 3.5, 3.25) may be used.

3-7-5-3. Instrumental evaluation

Wrinkles are to be measured to calculate wrinkle analysis parameters at baseline and each measuring time point using two-dimensional image analysis of skin replicas with oblique lighting, three-dimensional analysis of skin replicas or *in vivo* (direct) three-dimensional analysis.

3-8. Participant questionnaire

Participant questionnaire surveys are to be conducted as necessary to monitor problems concerning product use, how the product is used, and product efficacy.

3-9. Adverse events and adverse drug reactions

Adverse events (AEs) mean any and all undesirable events occurring during the trial period, regardless of causal relationships with the test sample. Adverse drug reactions (ADRs) mean undesirable events that occur after using the test sample, in which a causal relationship with the test sample cannot be ruled out.

For any and all AEs and ADRs, details of onset and course, seriousness, treatment given and its details, and prognosis (post-treatment course) are to be documented. Causal relationship with the test sample is to be determined by a physician involved in the study.

3-10. Efficacy analysis

With appropriate statistical analysis methods, changes in all endpoints during the trial period from baseline (before test sample application) to the end of the study in the active ingredient group are to be compared with those in the placebo group. Relevant data should desirably be excluded from the analysis in the event any of the following occur:

(1) Inappropriate product usage such as extremely infrequent use
(2) Occurrence of an AE or an ADR during the trial period that prevents continuation of trial
(3) Compromised data reliability due to use of concomitant drugs, etc.

Product efficacy is to be analyzed in participant groups from which those to whom any of the exclusion criteria above apply have been excluded. Product safety is to be analyzed in all participants who used the test sample.

3-11. Overall efficacy evaluation

Product efficacy is to be determined based on an efficacy analysis that demonstrates significant wrinkle reduction ($p < 0.05$) in visual assessment or photographic evaluation or significant differences ($p < 0.05$) in wrinkle analysis parameter changes in the active ingredient group compared with the placebo group.

3-12. Ethics

Studies are to be conducted in compliance with "Ethical Guidelines for Clinical Research (MHLW Announcement No. 255, 2003)" dated July 30, 2003. Review by and approval of an ethical review board and voluntary written consent of participants are mandatory in any study. The proper storage and management of information is to be implemented to ensure the thorough protection of personal data.

4. Summary

The Task Force Committee for Evaluation of Anti-Aging Function has developed a guideline for evaluation of products with anti-wrinkle functions the efficacies of which have not been confirmed by the regulatory authority in Japan. Prior to developing the guideline, current wrinkle measurement methods and study reports on efficacies of anti-wrinkle products were reviewed and the attitudes of general consumers, dermatologists, and pharmaceutical researchers toward wrinkles were surveyed[12]. Evaluation criteria and descriptions of efficacies were separately discussed and determined for cosmetic-level efficacy and quasi-drug-level efficacy based on the survey results as shown in Table 1. Specifically, moisture retention in the stratum corneum was considered to be the action mechanism of cosmetics, and quasi-drugs were considered to have other action mechanisms. Efficacies of respective products were to be described as "diminishes wrinkles due to dryness" and "improves wrinkles." Efficacy evaluation criteria were also determined separately for the products belonging to the two different categories. As a prerequisite for claiming a quasi-drug-level efficacy, a description of the action mechanism to improve wrinkles is required. Table 1 is therefore the essence of the guideline, showing its basic concept.

Technologies used in wrinkle measurements are advancing rapidly. It is reasonable to assume that new methods will be developed to replace the current methods described herein in the future. Development of improved bases and active ingredients for wrinkle improvement will also be developed, possibly resulting in changes to the descriptions of efficacies proposed herein. Contents of the guideline should be reviewed and revised in line with such future advances.

Table 1. Concept of Evaluation of Anti-Wrinkle Cosmetics and Quasi-Drugs and Relevant Matters

	Cosmetics	Quasi-drugs	Drugs (reference)
(1) Wrinkle area	Outer corner of the eye	Outer corner of the eye	All areas including outer corner of the eye (including glabella and nasolabial groove)
(2) Recommended participants	Participants with Grade 1 to 3 wrinkles	Participants with Grade 3 to 5 wrinkles	No specific recommendation
(3) Evaluation method	Blinded (Treatment/non-treatment is masked from evaluators)	Double-blind	-
	Comparison between the treatment group and the non-treatment group	Comparison between the active ingredient group (or application sites) and the placebo group (or application sites) * For application site comparison, wrinkles at the outer corners of the left and right eyes are subject to evaluation.	-
(4) Endpoints	• Visual assessment and photographic evaluation using the wrinkle grade standard • Two-dimensional or three-dimensional instrumental evaluation of replicas or *in vivo* three-dimensional instrumental evaluation	• Visual assessment and photographic evaluation using the wrinkle grade standard • Two-dimensional or three-dimensional instrumental evaluation of replicas or *in vivo* three-dimensional instrumental evaluation	-
(5) Concept of efficacy evaluation	Significant difference in wrinkle reduction shown by the visual, photographic or instrumental evaluation	Significant difference in wrinkle improvement shown by the visual assessment or photographic and instrumental evaluation	-
(6) Trial period	At least 2 weeks	At least 2 months	No specific recommendation
(7) Description of efficacy	Diminishes wrinkles due to dryness	Improves wrinkles	Treats wrinkles
(8) Wrinkle reduction mechanism	Not required	Required (Not including mere water/moisture retention in the stratum corneum)	Required

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Appendix 1. Guideline for Wrinkle Photography

1. Introduction

The Guideline for Wrinkle Photography was developed with following objectives when taking photographs for wrinkle evaluation.

- To ensure reproducible photography sessions and to minimize differences in photographing conditions when wrinkle photographs are taken at multiple sessions (e.g. baseline and final sessions) over the course of a study
- To ensure that images are obtained for photographic wrinkle evaluation at all photographing sessions
- To provide a guideline for non-professional photographers to take photographs with professional-level quality, thereby enabling objective wrinkle evaluation in general.

The guideline therefore recommends a photographing procedure in which a commonly used regular camera is used; however, other photographic devices may be used as long as said three objectives are achieved. The conditions described in the subsequent section need to be satisfied in all photographing procedures.

2. Photographing Conditions

2-1. Equipment

- Lighting with minimum light-dark contrast that reduces shine on skin surface
- Camera position and angle that ensures uniform image of wrinkle observation area and avoids defocusing
- Complete consistency of equipment conditions is to be ensured before and after the trial

2-2. Environment

- A room where the environment (temperature, humidity) can be regulated at a constant level as much as possible is to be used while maintaining the same environmental conditions throughout the study.

2-3. Participants

- Photographs are to be taken after the skin of participants adapts to the environment in the photography room (n accordance with the adaptation time specified in Guideline for Evaluation of Anti-Wrinkle Products). Uniform skin adaptation is to be ensured.
- The head of the participant is to be held steady with a chin support to provide facial support.
- Participants are to be advised to close their eyes lightly.

2-4. Other condition

- A reference guide for image correction is to be included in photographs for correction of differences in multiple pictures.

3. Photographing with camera (recommended)

3-1. Equipment

3-1-1. Camera

Recommended camera hardware includes a single-lens reflex digital camera and a macro (micro) lens (35-mm equivalent focal length of 60 to 105 mm). For an APS camera (about 24 × 16 mm), resolution of at least 2.5 million pixels will be sufficient (equivalent to Nikon D1).

White balance of the camera is to be adjusted to the lighting environment. For example, the white balance mode that corresponds to speed light photography is recommended. The shutter speed and aperture value are to be set to focus on the entire wrinkle observation area so that defocusing of the outer corner of the eye can be avoided. The set speed and value should be checked before taking photographs. The larger the aperture value is, the wider the area that comes into focus.

Resolution equivalent to Fine Mode/JPEG (1/4) compression of a Nikon single-lens reflex digital camera will be sufficient to take photographs for wrinkle evaluation.

The camera is to be set at an angle so that the wrinkle observation area at the outer corner of the eye is shown as a flat surface in the photograph; however, the camera position needs to be finely adjusted for each participant. Wherever possible, the camera should be maintained at a consistent height.

Photographs are to be printed in 2L size and used for wrinkle evaluation. Wrinkles will be clearly shown and easily evaluated in photographs in 2L size or larger. To ensure

even high quality and consistency, printing of photographs using a personal printer should desirably be avoided.

3-1-2. Lighting

Use of umbrella strobes is recommended to minimize the effect of skin shine; however, a ring strobe attached to the camera lens may be used as an alternative. Although an umbrella strobe minimizes the effect of skin shine, it requires a large space for set-up that could be troublesome. On the other hand, while a ring strobe is easy to set up, it causes skin shine.

The positions of umbrella strobes are to be determined in relation to the camera set-up to ensure sufficient exposure. The angle of lighting from the umbrella strobe is to be downward to minimize the effect of skin shine. This point should also be considered when determining the strobe position.

An example of an umbrella strobe layout is shown in Fig. 1.

[Plan view] [Layout example]

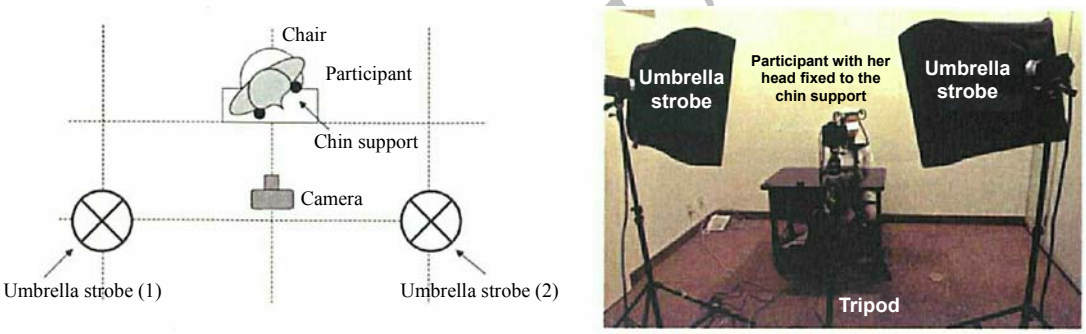

Fig. 1. Layout Example of Wrinkle Photography

3-2. Environment

A room in which a constant temperature and humidity can be maintained by controlling the environment is recommended. The temperature and humidity must be set in accordance with the conditions specified in Guideline for Evaluation of Anti-Wrinkle Products. Desirable temperature/humidity is 20 to 25°C/50 ± 5%, which must remain unchanged during the study.

3-3. Participants

Use of a chin rest to stabilize the face of participant is recommended to minimize any shift in angle. For example, a chin support such as the one made by Takei Scientific Instrument Co., Ltd. shown in Fig. 2 used for ophthalmologic examinations is simple to

use. Use of the chin support manufactured by Takei Scientific Instrument Co., Ltd. is shown in Fig. 3. Note that some types of chin support may block the view of the observation area such as the outer corner of the eye. Participants are to be instructed to close their eyes lightly as opposed to tightly.

Fig. 2. Chin Support (Takei Scientific Instruments Co., Ltd.)

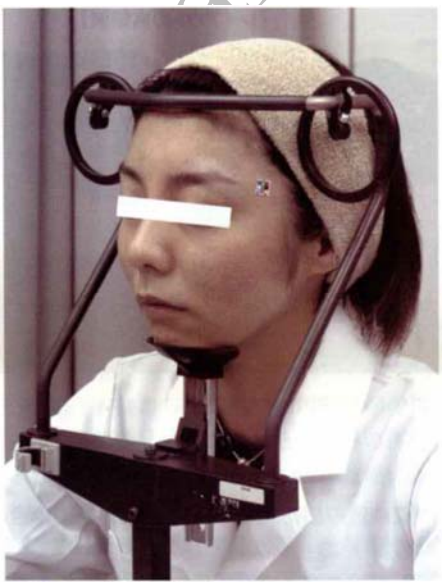

Fig. 3. Use of Chin Support

3-4. Simultaneous photographing of reference for image correction

A photo scale or a color chart for image or scale correction is to be attached near the wrinkle observation area where it will not affect subsequent photographic evaluation. For example, a reference is attached to the temple. See Fig. 4 for examples of photo scale and color chart.

Fig. 4 Color Chart for Image Correction CASMATCH,
BEAR Medic Corporation

3-5. Area of wrinkle photography

It is recommended that photographs be taken of the area where wrinkles at the outer corner of the eye can be evaluated and the participant's identity is not revealed to ensure that the participant's portrait right is not violated. For example, the area that covers the lightly closed eye and the hairline around the ear is photographed as shown in Fig. 5, and evaluation is made based on the area from the lower half of the eye and below.

4. Wrinkle Photography Procedure

An example of the wrinkle photography procedure follows:

1. Have the participant wash her face to remove makeup.
2. Usher the participant into the photo-shooting environment [a room with constant temperature and humidity (controlled environment)] and have her wait for at least 15 minutes to let her skin adapt to the environment.
3. Attach a photo scale/color chart near the observation area of the participant's face.
4. Seat the participant and instruct her to put her chin on the chin support.
5. Make slight adjustments to the camera position so that the wrinkle observation area at the outer corner of the eye comes into the desirable position in the camera frame.
6. Photographing. Take several photographs while checking the focus repeatedly to avoid failure such as defocusing.
7. Print the photographs in 2L size, for example, and use them for wrinkle evaluation.

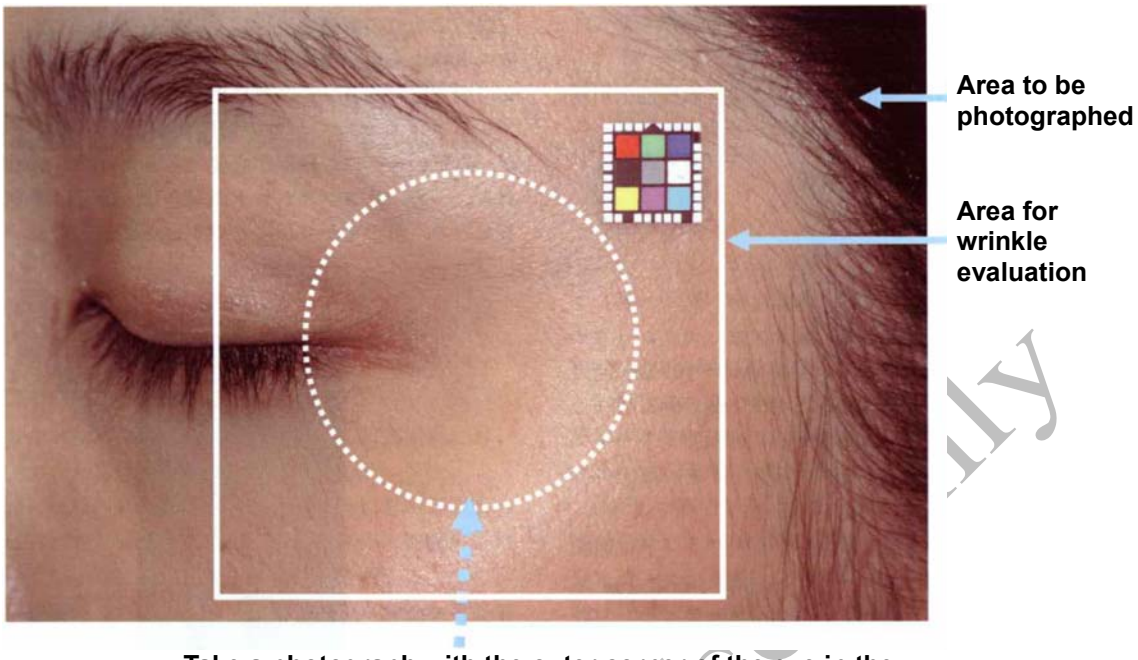

Fig. 5. Area for Wrinkle Photography

Appendix 2. Guideline for Wrinkle Measurement

1. Introduction

The Guideline for Wrinkle Measurement was developed with the objective of standardizing wrinkle measurement using instruments. Of various measurement methods developed so far, measurements allowing reproducibility of wrinkle shape data, measurement accuracy, and data analyzability were selected. After conducting surveys on overseas contracted testing institutions and instrumental measurement tests initiated by the Task Force Committee for Evaluation of Anti-Aging Function, and by referring to the Guideline for Wrinkle Evaluation[1)] developed by Japanese Cosmetic Science Society in 1998, the following three measurement methods were selected.

- Two-dimensional image analysis using replicas and oblique lighting
- Three-dimensional image analysis using replicas
- *In vivo* (direct) three-dimensional analysis

2. Wrinkle Analysis Using Replicas

Wrinkle replicas of the outer corner of the eye are created to measure and analyze the wrinkle shape. In this section, "replica sampling," "two-dimensional image analysis using replicas and oblique lighting," and "three-dimensional image analysis using replicas" are described separately.

2-1. Replica sampling

2-1-1. Replica material

SILFLO (Flexico, England) and EXAFINE (GC, Japan) with which fine skin surface shapes can be replicated are recommended based on their wide use in replica sampling.

2-1-2. Environmental conditions for replica creation

After having the participant thoroughly adapt to the constant temperature and humidity in the room, create a skin replica of the seated and rested participant with the eyes lightly closed.

2-1-3. Wrinkle sample collection area

Collect a wrinkle sample in the area of at least 10 mm × 10 mm and about 5 mm away from the edge of the eye (see Fig. 1).

2-1-4. Precautions for replica sampling

Keep in mind the difference in physical properties and polymerization/solidification time to ensure accurate wrinkle replica sampling.

- Do not stir in bubbles when mixing the mold material.
- Peel off the solidified replica material carefully.

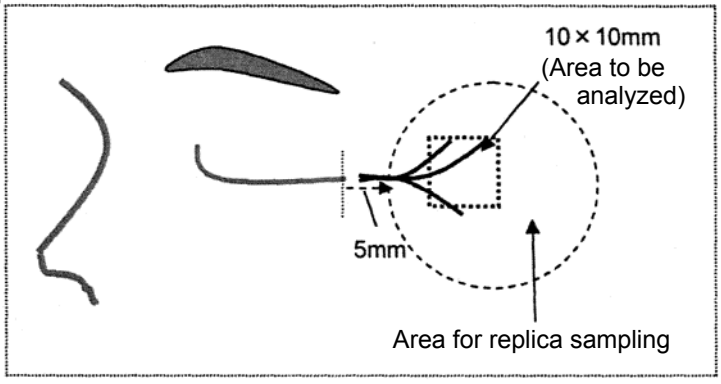

Fig. 1. Replica Sampling Site and Area for Wrinkle Analysis

2-2. Two-dimensional image analysis using replicas and oblique lighting

A wrinkle replica sample of the outer corner of the eye is exposed to downward directed light at a specific oblique angle with respect to a line drawn parallel to the skin surface and perpendicular to the predominant wrinkle direction, and the image of the shadows is analyzed using various parameters[2)3)].

The specific instrumental configuration and measurement principle are described below.

2-2-1. Device configuration

Diagram of image input and analysis system is shown in Fig. 2. The system consists of the following three devices.

(1) Light projection device

The device consists of a light source that uses optical fibers to direct light from a halogen lamp or a xenon lamp perpendicularly to the wrinkle direction in the replica and at a certain angle (20 to 30 degrees) to the plane of the skin, and a platform for replica fixation.

(2) Image input device

Projected image of the replica is magnified at a given power (about × 30) by using a stereomicroscope. The image information is converted to digital signals by a CCD camera and transmitted to the image analysis device described below.

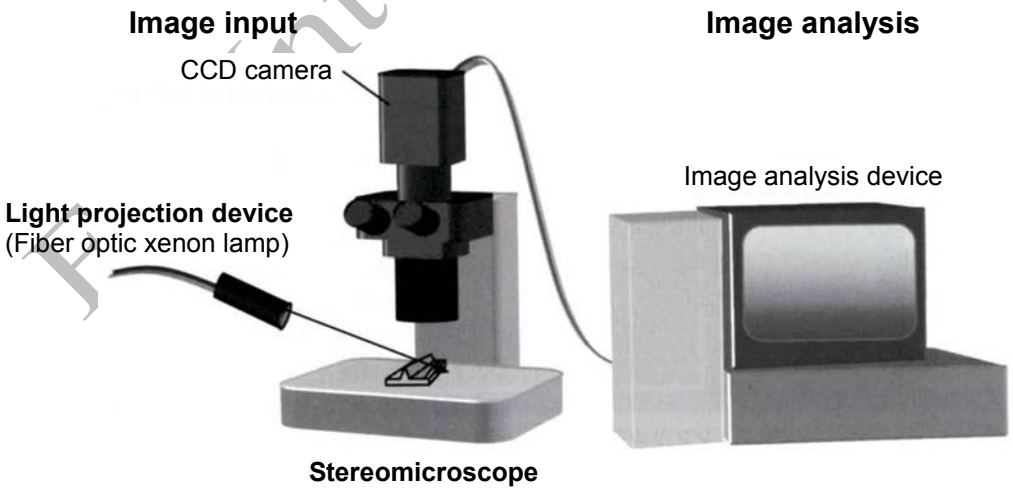

Fig. 2. Device for Wrinkle Image Analysis Using Oblique Light

(3) Image analysis device

The device consists of an exclusive image analysis instrument or a personal computer with image analysis software (e.g. Winroof-Pro, IPLab, Solution Systems).

2-2-2. Measurement principle

The shadows of the convex portions of the replica (wrinkle sample) created by light projection described above are picked out to measure the wrinkle depth and area ratio based on the wrinkle area and width (Fig. 3).

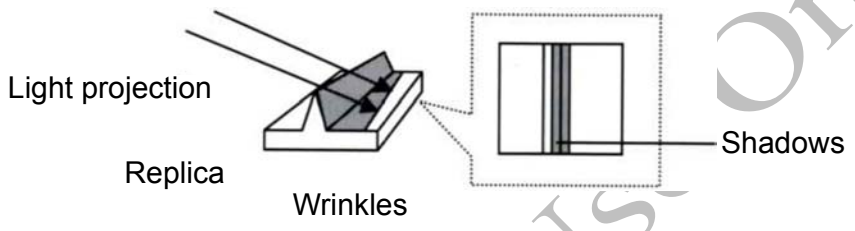

Fig. 3. Projected Image of Wrinkle Replica

2-2-3. Wrinkle position adjustment in two-dimensional image analysis using replicas and oblique light

When comparing pre- and post-application wrinkle samples for evaluation of the wrinkle improving effect of the test product or cosmetics with supposed efficacy, position adjustment will be necessary to analyze specific wrinkles duplicated on the pre- and post-application replicas. Wrinkle position may be adjusted based on the wrinkle features themselves or a landmark other than wrinkles such as a mole. Image analysis software for position adjustment may come with the device or may need to be developed originally.

2-2-4. Wrinkle analysis method

Wrinkles are to be analyzed according to the following procedures.

(i) Binary image processing

When a light is shed on a replica, various types of shadows (e.g. dark and large, small and fine) are projected. Binary image processing is required to pick out dark and large shadows that are considered to be wrinkles. Specifically, brightness is converted into binary data. For example, brightness that exceeds the specific threshold is converted into 255 (white) and that below the threshold into 0 (black) to pick out shadows with darkness exceeding the threshold. Binary

processing enables the subsequent analyses.

The threshold for binary processing may vary depending on individual replicas (wrinkles) or may be consistent. Specifically, different thresholds are used for separate analyses of large wrinkles and small wrinkles or all types of wrinkles are analyzed based on a specific threshold and conditions. Use of a threshold depends on how the measurer defines the initial condition.

Some studies reported correction of lighting irregularity by inverse Fourier transform to remove the Fourier transform-computed low-frequency light computed before binary processing. A processing program such as this is installed in the image analysis system described earlier.

(ii) Calculation of wrinkle analysis parameters

It is desirable to use the following parameters for wrinkle analysis.

(1) Wrinkle area ratio

Based on the total area of wrinkle-associated shadows obtained in accordance with the basic principle shown in Fig. 3, the ratio of wrinkle area to the entire area for analysis (10 mm × 10 mm) is calculated (wrinkle area ratio).

(2) Wrinkle depth

Wrinkle depth is to be calculated based on the area (s) and length (l) of shadows of the convex portions of replica (wrinkle sample) created by the light as follows (Fig. 4).

(2)-1. Mean total wrinkle depth

Depths of all wrinkles in the area for analysis are calculated as shown in Fig. 4. The mean depth is used as the mean total wrinkle depth.

(2)-2. Mean maximum wrinkle depth

The wrinkle that produces the largest shadow area is used as the largest wrinkle. The depth of such wrinkle obtained based on the calculation shown in Fig. 4 is used as the mean maximum wrinkle depth.

(2)-3. Maximum depth of largest wrinkle

The depth calculated in the following formula based on the maximum width of the shadow of the largest wrinkle described in (2)-2 (d, see Fig. 4) is used as the maximum depth of the largest wrinkle.

Maximum depth of largest wrinkle = $d \times \tan \theta$

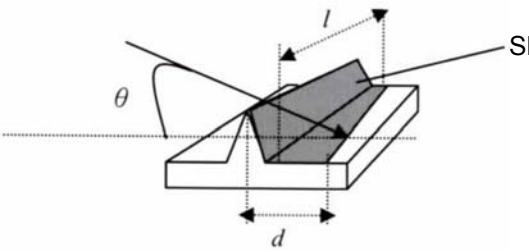

Fig. 4. Wrinkle Depth Measurement Based on Projected Image of Replica

2-2-5. Precautions for two-dimensional image analysis using replicas and oblique lighting

(1) Precautions concerning replicas

In analyses using the wrinkle analysis system described above, large curves in replicas associated with facial contours may prevent accurate quantitative analyses. It is therefore desirable to process replicas to minimize distortion and deflection as much as possible. Various processing methods are available. One way to obtain replicas with a flat baseline and no excessive deflection is to carve out a replica slightly larger than the area for analysis and make adjustment by placing a supporting material (e.g. glass plate) on the back.

(2) Precautions for handling replicas with large and small wrinkles

When large wrinkles and small wrinkles are mixed, small wrinkles may be hidden in the shadows of large wrinkles and excluded from the analysis. The effect of large wrinkles needs to be reduced by considering adjustment of the direction of the light falling on the replica (from which side the light should be directed onto the wrinkles).

2-3. Three-dimensional analysis using replicas

Replicas of wrinkles at the outer corner of the eye are analyzed based on three-dimensional data. In the three-dimensional wrinkle analysis, higher precision can be expected compared with the two-dimensional image analysis using oblique lighting described in 2-2.

Devices used in the analysis should desirably satisfy the following specification criteria.

- Wrinkles can be measured in an area of about 10 mm × 10 mm.
- *XY* resolution is 50 μm, and *Z* resolution is 5 μm or below.

- Wrinkle position adjustment is necessary in pre- and post-application replicas for wrinkle analysis. Therefore, the device should allow the testing person to check and compare replica sampling positions.

Three methods of three-dimensional measurement that satisfy the aforementioned criteria are described below.

2-3-1. Three-dimensional measurement using laser focus displacement meter

Using a laser focus displacement meter employing the "confocal principle," according to which the measurement is based on the lens focal length, three-dimensional information is obtained by moving the *XY* stage on which the measurement subject is placed back and forth and around.

2-3-1-1. Device configuration

An example of device configuration is shown in Fig. 6. The main system consists of the following three devices.

(1) Laser focus displacement meter
(2) *X/Y* stage and stage controller
(3) Personal computer (PC) for device control

2-3-1-2. Measurement principle of laser focus displacement meter

As shown in Fig. 7, a laser focus displacement meter employing the "confocal principle" is used to measure surface features from the focal length of the lens. (1) The light from the laser passes through the objective lens, which is vibrated in the vertical direction by a tuning fork and is focused on different levels of the object as it moves; (2) the light reflected from the object goes through the half-silvered mirror and the pinhole and reaches the light-sensitive element; (3) the reflected laser light that forms a focused image passes through the pinhole, while the more widely spread out-of-focus light is blocked. The distance to the object is measured by knowing the position and focal length of the lens at each instant, and the geometry of the optical setup. This type of device is called a "confocal microscope" by its inventor because of its optical design.

2-3-2. Three-dimensional measurement using light-section method

A three-dimensional digitizer that employs the light-section method with laser slit light as its measurement principle is used for three-dimensional measurement[4)5)]. The measurement time can be substantially shortened with this method compared with that using the laser focus displacement meter described in the previous section. The specific device configuration and measurement principle used for this method are described below.

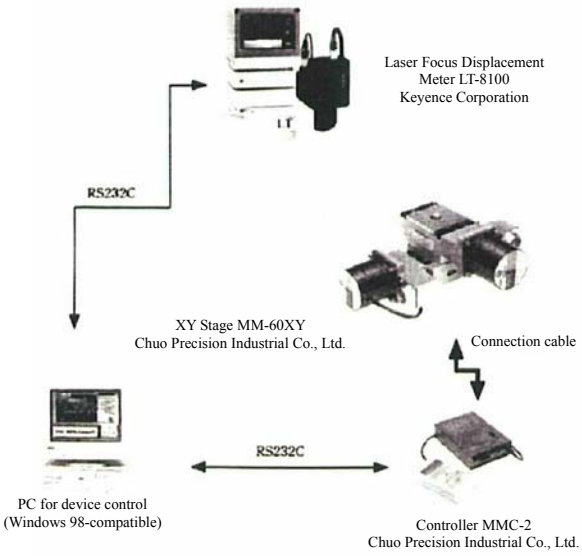

Fig. 6. Laser Focus Displacement Meter System

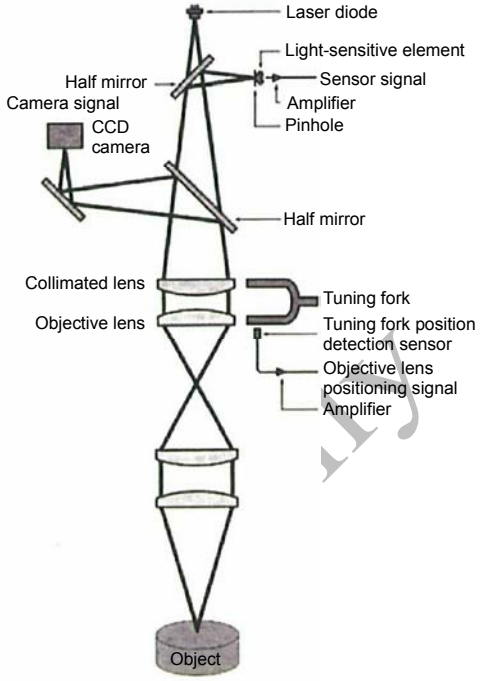

Fig. 7. Principle of Laser Focus Displacement Meter

[Figs. 6 and 7 excerpted from User's Manual of Laser Focus Displacement Meter LT8100 (Keyence Corporation)]

2-3-2-1. Device configuration

An example of the device configuration is shown in Fig. 8. The system mainly consists of the following four devices.

(1) Probe head
(2) Scanner driver
(3) Image encoder
(4) Personal computer for device control

2-3-2-2. Principle of three-dimensional measurement using the light-section method

The measurement system employs the "light-section method with laser slit light," one of the noncontact optical methods.

Laser slit light is scanned on the entire surface of the object. The surface curves are represented by three-dimensional coordinates using the triangulation principle based on the reflected light. The measurement principle is described below in line with the measurement concept shown diagrammatically in Fig. 9.

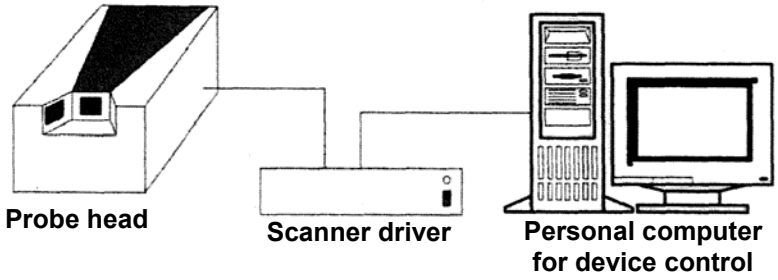

Fig. 8. Device for Three-Dimensional Measurement with Light-Section Method
(Excerpted from the specification of VOXELAN HEV-50HS of Hamano Engineering Co., Ltd.)

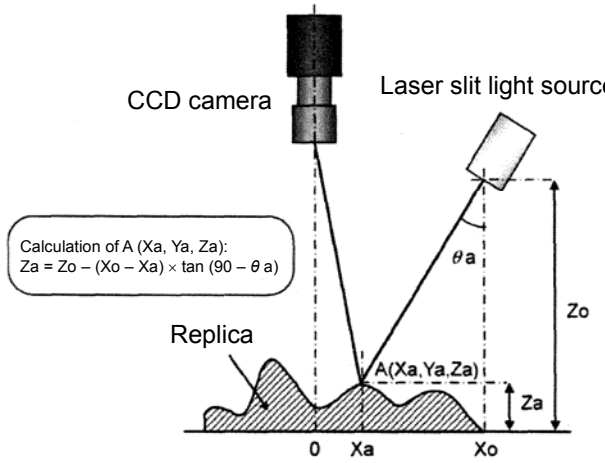

Fig. 9 Simplified Diagram of Measurement Principle

Laser slit light converted to a slit shape (line) is scanned on the replica surface. The CCD camera placed above the object catches the illuminated image. From the laser slit light-illuminated image caught by the CCD camera, the three-dimensional coordinates of the entire shape are calculated using the formula shown in Fig. 9 based on the triangulation principle. The three-dimensional coordinates of the entire shape are obtained by scanning the laser slit light on the entire surface based on the principle described above.

2-3-3. Three-dimensional measurement using lattice pattern projection

A lattice (stripe) pattern is projected onto the object, which is measured from an angle that is different from the direction of the projected light. The projected pattern will be distorted depending on the surface contour of the object (Fig. 10). The distortion is analyzed to obtain three-dimensional information on the object surface. The measurement time can be further shortened with this method compared with the light-section method described in the previous section. The major instruments for this

form of skin surface measurement method include PRIMOS of GFM (Germany) and dermaTOP-Blue of Breuckmann (Germany). Both instruments employ the same basic principle, and in this section measurement with PRIMOS is described.

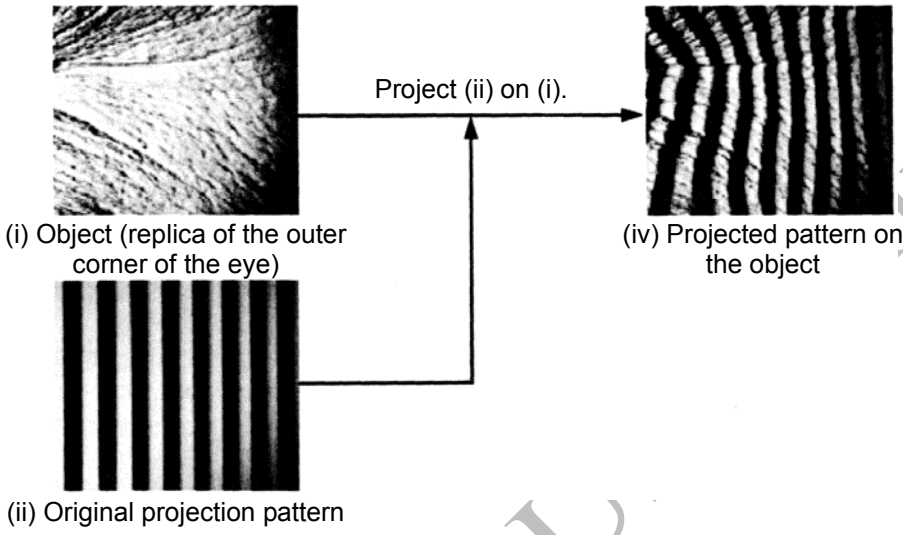

Fig. 10. Distortion of Projected Pattern on Replica of Outer Corner of Eye
(Photographs excerpted from Jaspers, et al.: XXIst IFSCC Congress, Berlin, 430-434, 2000)

2-3-3-1. Device configuration

The measurement system (PRIMOS) consists of the following three devices.

(1) 3D analysis device (lattice pattern projection device, CCD camera, etc.)
(2) Desktop computer system and display for device control
(3) Measurement and analysis software supplied with PRIMOS of GFM (Germany)

2-3-3-2. Principle of three-dimensional measurement using lattice pattern projection

An evenly spaced lattice (stripe) pattern is projected onto the object, which is measured from an angle different from the direction of the projected light with the CCD camera as shown in Fig. 11. The same straight lattice pattern as the original is obtained if the object is flat; however, the stripe pattern will be distorted if the surface of the object is uneven (see Fig. 10). The distortion is analyzed to obtain three-dimensional information on the object surface[6)7)].

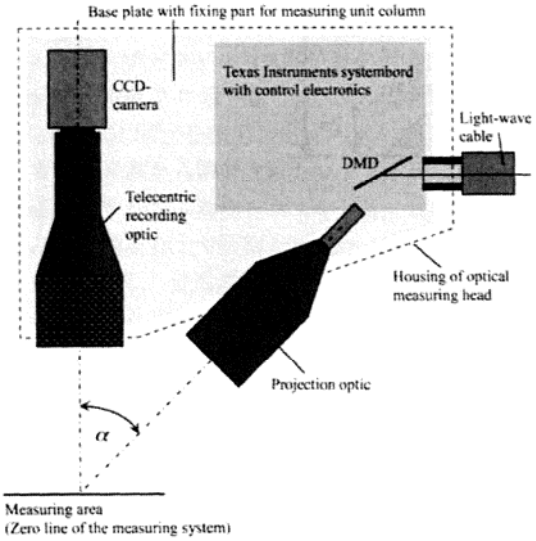

Fig. 11. Optical System of PRIMOS
[Excerpted from the user's manual of the 3D analyzer PRIMOS of GFM (Germany)]

2-3-4. Wrinkle position adjustment in three-dimensional analysis of replicas

When comparing pre- and post-application wrinkle samples for precise wrinkle analysis in clinical studies on cosmetics, position adjustment will be necessary. Wrinkle position may be adjusted based on the wrinkles themselves or skin features other than wrinkles in the three-dimensional analysis of replicas by observing the entire object with a CCD camera. When using a measurement device without a position adjustment function with a CCD camera, observation of the entire object becomes possible by attaching an additional lighting device, for example. Position adjustment can be made easier by creating an image of wrinkles accentuated by shedding light on wrinkles at an oblique angle. Positions of areas for wrinkle analysis can also be adjusted on the monitor by comparing three-dimensional images obtained based on extensive three-dimensional information derived from replicas.

2-3-5. Wrinkle analysis

Wrinkles are analyzed in accordance with the following procedure.

(i) Replica shape correction

The shape of the replica must be corrected, because its three-dimensional shape includes the slope of the entire replica along with any distortion. Common correction methods are described below.

- In the low-frequency domain, any large swell component is removed by using

Fourier/inverse Fourier transforms for reconfiguration.

- The first to fifth regression planes (large swell components) are obtained and removed from the replica shape.
- Large sloping/swell components are obtained by using a Gaussian filter and removed from the replica shape.

(ii) Picking out wrinkle area

A threshold is determined at a certain height based on the corrected replica shape. Areas higher than the threshold are picked out as wrinkle areas. A threshold is generally determined based on the minimum depth of the wrinkles to be evaluated.

(iii) Calculation of wrinkle analysis parameters

It is desirable to use following parameters for wrinkle analysis.

(1) Wrinkle area ratio

Wrinkles are picked out from the corrected three-dimensional shape. The ratio of the wrinkle area to the entire measurement area is used as the wrinkle area ratio.

(2) Mean total wrinkle depth

Wrinkles are picked out from the corrected three-dimensional shape. The mean depth of wrinkles in the measurement area is used as the mean total wrinkle depth.

(3) Mean maximum wrinkle depth

Wrinkles are picked out from the corrected three-dimensional shape. The mean depth of wrinkles in the measurement area with the maximum volume (or area) is used as the mean maximum wrinkle depth.

(4) Maximum depth of largest wrinkle

Wrinkles are picked out from the corrected three-dimensional shape. The maximum depth of wrinkles in the measurement area with the maximum volume (or area) is used as the maximum depth of the largest wrinkle.

(5) Total wrinkle volume

Wrinkles are picked out from the corrected three-dimensional shape. The volume of each wrinkle in the measurement area is calculated, and the sum of the volumes of all the wrinkles is used as the total wrinkle volume.

(6) ISO standard surface roughness parameters (R_a, R_z, R_y)[8)]

- Arithmetic mean of roughness curve (R_a)

Mean absolute distance from the average line to the curve

- Ten-point average of roughness curve (R_z)

  Sum of the mean of the 5 highest peaks and the 5 deepest creases (distance)

- Maximum height of roughness curve (R_y)

  Distance between the highest peak and the deepest crease

3. *In vivo* (direct)Three-Dimensional Analysis

Various wrinkle-related parameters are analyzed based on *in vivo* (direct) three-dimensional measurements of wrinkles at the outer corners of the eyes of human without creating replicas. One of the disadvantages of *in vivo* measurement is that the body of the participant cannot be immobilized completely. Measurement needs to be completed within a short time since the effect of pulse and slight body movement cannot be avoided, even if the measurement site is immobilized with some form of apparatus. Three-dimensional measurement using lattice pattern projection is one such method. *In vivo* skin measurement devices for this purpose include PRIMOS and dermaTOP-Blue described in 2-3-3. Instant measurement (under 1 second) is possible with these devices.

3-1. Three-dimensional measurement using lattice pattern projection

See 2-3-3.

3-1-1. Device configuration

See 2-3-3-1.

3-1-2. Measurement principle

See 2-3-3-2.

3-2. Wrinkle position adjustment in *in vivo* (direct) three-dimensional analysis

In wrinkle analyses, pre- and post-application wrinkle position adjustment is necessary. Unlike replica methods, complete position adjustment is impossible in direct *in vivo* measurement since consistency of measurement conditions (e.g. facial angle) cannot be ensured even when a fixing apparatus is used. Therefore, software that enables wrinkle position adjustment based on pre- and post-application three-dimensional data is to be used (the measurement software supplied with PRIMOS has a position adjustment function). Position adjustment is still required to a certain extent during measurement since position adjustment and analysis are impossible if the pre- and post-application

three-dimensional data do not include the same measurement area.

3-3. Wrinkle analysis

Wrinkles are analyzed in accordance with the following procedure.

(i) Shape correction

The shape is corrected prior to analysis since the three-dimensional shape includes the slope of the entire replica as well as any distortion. Common correction methods are described below.

- In the low-frequency domain, any large spreading factor is removed using Fourier/inverse Fourier transforms for reconfiguration.
- The first to fifth regression planes (large spreading factors) are obtained and removed from the three-dimensional shape.
- Large slant/spreading factors are obtained by using a Gaussian filter and removed from the three-dimensional shape.

(ii) Picking out wrinkle area

A threshold is determined at specified height based on the corrected three-dimensional shape. Areas higher than the threshold are picked out as wrinkle areas. A threshold is generally determined based on the minimum depth of the wrinkles to be evaluated.

(iii) Calculation of wrinkle analysis parameters

See 2-3-5 C.

3-4. Precautions for *in vivo* (direct) three-dimensional analysis

Comparison of data obtained in the same area based on the *in vivo* (direct) method and the three-dimensional measurement of replicas revealed that the former was affected by the movement of participants' bodies during measurement and that shallow wrinkles with absolute depths of about 40 to 50 μm or below were difficult to measure (data reviewed by Task Force Committee for Evaluation of Anti-Aging Function). However, actual wrinkle measurement will not be a problem since the minimum skin contour (shape) recognized as wrinkles have a depth of at least about 100 μm according to a separate investigation.

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8) JIS B 0601, Surface Roughness – Definition and Labeling

<Cosmetics Evaluation Guidelines>

Guideline for Evaluation of New Whitening Quasi-Drug Products

Task Force Committee for Evaluation of Whitening Function*

1. Introduction

Skin pigmentation and other concerns related to skin tone such as "spots/freckles" are always at the top of the list of skin problems consumers complain about in questionnaires. Consumer expectations for whitening cosmetics are high in proportion to the degree of such skin problems. In fact, the market for whitening cosmetics has been growing in Japan.

Whitening cosmetics are classified as quasi-drugs according to the Pharmaceutical Affairs Law. Regulatory approval for the efficacy of whitening cosmetics has so far been granted to only preventive effects on spots and freckles. Specifically, the effectiveness of a whitening cosmetic product may be described as "prevents spots/freckles due to sunburn" or "prevents spots/freckles by inhibiting production of melanin" (alternative)[1]. However, consumers may expect whitening cosmetics to not only prevent spots/freckles but also to reduce existing spots/freckles. The questionnaire survey conducted by the Task Force Committee for Evaluation of Whitening Function (hereafter, "Committee"), a subcommittee of the Japanese Cosmetic Science Society's Cosmetics Evaluation Committee, revealed that whitening cosmetics were expected to "eliminate spots/freckles" and "diminish spots/freckles"[2].

With the significant advances made in scientific technologies, substantial knowledge about the mechanism and regulation of melanin pigment production has been accumulated. Technologies for physical measurement of skin surface conditions and skin tone have also dramatically advanced. Production of whitening cosmetics with novel efficacies has started to become feasible due to advances in technology; for example, promising outcomes have been reported from studies that evaluated improvement in skin pigmentation[3-26].

In order to promote actual production of "evidence-based cosmetics," the

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Committee worked on "development of Guideline for Evaluation of New Whitening Quasi-Drug Products." Evidence that strongly support product effectiveness should be based on appropriate evaluation. The objective of the Committee was to conduct more appropriate studies on the items and content of the guideline based on literature on whitening cosmetics and questionnaire surveys. Specifically, selection of study participants and efficacy evaluation criteria were comprehensively discussed and established as guideline items. Descriptions of efficacies recommended by the Committee are also mentioned in this report.

As mentioned earlier, the advancement of scientific technologies has been remarkable. The current guideline will not necessarily be appropriate at all times and may need to be revised as necessary in the future. The guideline aims to provide the basics required for evaluation methods. It should be noted that individual studies require different protocols with the details thereof appropriate to the specific purpose.

2. Guideline for Evaluation of New Whitening Quasi-Drug Products

2-1. Target pigment anomaly and study participants

Healthy male and female persons with superficial pigmentation (e.g. chloasma, senile pigment freckles, ephelides, post-inflammatory pigmentation including sunburn) are to be enrolled. Deep pigment anomalies such as nevus of Ota are to be excluded.

Persons to whom any of the following applies are to be excluded.

1) Persons allergic to any cosmetic products
2) Persons receiving "hormone replacement therapy"
3) Pregnant women and breastfeeding mothers
4) Persons who have undergone any cosmetic procedures that may affect the intended application site
5) Persons whose participation in the study is otherwise considered inappropriate by physicians involved in the product evaluation

2-2. Study and study center

Studies are to be conducted under the management of a controller using the double blind method.

Studies are to be conducted in rooms where visual assessment, photographing, and

instrumental measurements can be conducted under specific conditions (in particular, it should be possible to make fine adjustments to the lighting conditions). When conducting a study at multiple study centers, ensure that measures to avoid inter-institutional errors and inter-observer errors are taken in advance.

2-3. Target application site and product application

Intergroup differences between an active ingredient group and a placebo (base) group are to be evaluated (half-face evaluation is acceptable if participants have symmetrical skin pigmentation on the left and right of their faces). Participants are to be randomly allocated to study groups while avoiding apparent biases in degree of skin pigmentation and age distribution.

Study products are to be "applied in the appropriate amount as necessary." Studies are to be conducted in accordance with guidelines for product use developed in advance. Test sample information such as composition, manufacturing method, and date of manufacture is to be retained for future follow-up investigation as necessary.

2-4. Provisions for concomitant drugs

Use of whitening products other than the study product and topical corticosteroids is to be avoided during the trial period. Use of oral vitamin C, vitamin E/C, steroid hormones, tranexamic acid, and contraceptives is to be avoided. Detailed information on concomitant drugs and cosmetics is to be documented in Case Cards.

Participants are to be instructed to avoid excessive exposure to ultraviolet rays during the trial period. Use of skin care products other than the study product is to be avoided or products not containing whitening ingredients are to be used if necessary. It is desirable to use the same product continuously during the trial period.

2-5. Duration of study

Ensure that the study is conducted for an adequate period of time (at least 1 month) to evaluate product efficacy.

2-6. Sample size

Based on preliminary studies, an appropriate sample size for efficacy evaluation is to

be determined. The determined sample size should enable discussion of study outcomes based on statistical data processing.

2-7. Evaluation and Measuring Methods

2-7-1. Endpoints

- Pre-application and post-trial visual assessment and photographing of identical application sites
- Pre-application and post-trial instrumental measurement of identical application sites
- Assessments are also to be conducted during the trial period as necessary.

2-7-2. Measurement conditions

(i) A room with a constant measurement environment (temperature, humidity, lighting) is to be used as much as possible. The conditions are to be kept constant during a measurement session.

(ii) Participants are to wash their faces to eliminate the effects of makeup.

(iii) Assessment/measurement is to be conducted after the participant's skin adapts to the environment (about 15 minutes).

(iv) The posture of the participant in the subsequent measurement sessions is to be the same as that in the initial measurement session.

(v) In so far as possible, assessments are to be conducted at the same time of the day.

2-7-3. Photographing procedure

(i) The area with skin pigmentation is to be photographed before the trial and at each assessment time point under the same conditions.

(ii) The magnification power and photographing angle are to be adjusted in subsequent photographing sessions based on the photographs taken before the trial in order to minimize variations in photographing angle.

(iii) A photo scale or a color scale (e.g. CASMATCH®) for color or scale correction is to be attached near the skin to be observed in a position where it will not affect later photographic evaluation.

2-7-4. Instrumental measurement

See Appendix "Guideline for Skin Pigmentation Measurement."

2-7-5. Skin pigmentation evaluation

See Appendix "Guideline for Skin Pigmentation Measurement."

2-7-5-1. Visual assessment

Visual assessment is to be conducted by dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with skin pigmentation evaluation) under the supervision of these dermatologists. A skin color chart may be used as an aid in visual assessments.

Evaluation:

(i) Pre-application and post-trial comparison

Visual skin conditions before the product application and after (or during) the trial are to be compared using a 5-scale evaluation: markedly improved, improved, somewhat improved, unchanged, and aggravated.

(ii) Two-site comparison in same participants (half-face evaluation)

Three-scale evaluation (apparently different, slightly different, and not different) of the difference between the two application sites

2-7-5-2. Photographic evaluation

Photographic evaluation is to be conducted by dermatological specialists, general dermatologists with equivalent clinical experience or other trained experts (researchers familiar with skin pigmentation evaluation) under the supervision of these dermatologists.

Evaluation:

(i) Pre-application and post-trial comparison

Photographs taken before the product application and after (or during) the trial are compared using a 5-scale evaluation: markedly improved, improved, somewhat improved, unchanged, and aggravated.

(ii) Two-site comparison in same participants (half-face evaluation)

Three-scale evaluation (apparently different, slightly different, and not different) of the difference between the two application sites based on the photographs of lateral application sites

2-7-5-3. Instrumental measurement

Differences between pre-application skin and skin at each measurement time point are to be evaluated based on reflectance spectrophotometry or equivalent optical measurement or digital image processing. Differences between two comparable sites are

to be evaluated in the half-face evaluation. The same instrument and measurement conditions must be used when a series of measurements is made. Data obtained using different instruments are not to be compared even for the same parameter.

2-8. Adverse events and adverse drug reactions

Adverse events (AEs) mean any and all undesirable events that occurred during the trial period, regardless of causal relationships with the test sample. Adverse drug reactions (ADRs) mean undesirable events that occurred after using the test sample, where a causal relationship with the test sample cannot be ruled out.

For any and all AEs and ADRs, details of onset and course, seriousness, treatment given and its details, and prognosis (post-treatment course) are to be documented. The causal relationship with the test sample is to be determined by a physician involved in the study. Events with possible causal relationships with the test sample are to be considered ADRs.

2-9. Participant questionnaire

Participant questionnaire surveys are to be conducted as necessary to monitor problems concerning product use, how the product is used, and product efficacy.

2-10. Efficacy analysis

With appropriate statistical analysis methods, changes in all endpoints are to be compared between the active ingredient group and the placebo (base) group. Relevant data should desirably be excluded from the analysis should any of the following occur:

(i) Inappropriate product usage such as extremely infrequent use

(ii) Occurrence of an AE or an ADR during the trial period that prevents continuation of the trial

(iii) Compromised data reliability due to use of concomitant drugs, etc.

Product efficacy is to be analyzed in participant groups from which those to whom any of the exclusion criteria above applies have been excluded. Product safety is to be analyzed in all participants who used the test sample.

2-11. Overall efficacy evaluation

Product efficacy is to be determined based on the efficacy analysis that demonstrates significant reduction of skin pigmentation ($p < 0.05$) in the active ingredient group compared with the placebo (base) group upon visual assessment or photographic evaluation and instrumental measurements consistent with the visual assessment or the photographic evaluation.

2-12. Ethics

Studies are to be conducted in compliance with "Ethical Guidelines for Clinical Research (MHLW Announcement No. 255, 2003)" dated July 30, 2003. Review by and approval of an ethical review board and voluntary written consent of participants are mandatory in any study. The proper storage and management of information is to be implemented to ensure the thorough protection of personal data.

3. Conclusion

Basic conditions for evaluation studies are provided in the "Guideline for Evaluation of New Whitening Quasi-Drug Products." The Task Force Committee for Evaluation of Whitening Function discussed proposals for novel efficacies and presented its ideas.

While the present efficacy of whitening cosmetic product may be described as "prevents spots/freckles due to sunburn" or "prevents spots/freckles by inhibiting production of melanin" (alternative), various proposals for new efficacy descriptions were made, including those in which words such as "alleviates" and "reduces" were used. The Committee reviewed the proposals with the collective intention of "developing a description suitable for quasi-drugs" and selected the description "gradually reduces skin pigmentation such as spots and freckles" as the Committee's proposal.

The proposal was selected based on the Committee's intention to imply a reduction in skin pigmentation since the "Guideline for Evaluation of New Whitening Quasi-Drug Products" provides guidance for evaluation of skin pigmentation-reducing effects and advises to avoid expressions that may suggest to consumers that these products are drugs and inform them of the gradual effect of the product in a straightforward manner. The proposal is introduced herein to present the Committee's idea of how a novel efficacy is to be described. The Committee hopes to continue further discussions with a view to

obtaining regulatory approval for a new efficacy for quasi-drugs.

The “Guideline for Evaluation of New Whitening Quasi-Drug Products” provides the basics for product evaluation. Thorough review of the details of study, development of an appropriate study protocol, and accurate analysis of study data will serve as the basis for producing evidence for a novel efficacy.

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Appendix: Guideline for Skin Pigmentation Measurement

1. Introduction

This guideline was developed to ensure higher accuracy of instrumental measurement of skin pigmentation.

2. Basics for Instrumental Measurement

Differences between pre-application skin and skin at each measurement time point are to be evaluated based on reflectance spectrophotometry or equivalent optical measurement or digital image processing. Differences between two comparable sites are to be evaluated using a half-face evaluation. The same instrument and measurement conditions must be used when a series of measurements is made. Data obtained using different instruments are not to be compared even for the same parameter.

Instruments:

1) Reflectance spectrophotometer
2) Tristimulus colorimeter
3) Erythema and melanin index meter or narrowband spectrophotometer
4) Skin image analysis system

3. Supplemental Information for Instrumental Measurement

Specific examples of measurement methods and data processing are described below for enhanced objectivity. However, the following instrumental measurement conditions and evaluation methods are not mandatory.

3-1. Measurement methods

1. For chloasma and large senile pigment freckles, measurement of spectral reflection factor, color (e.g. L*a*b*) or melanin index (MI) by contact instruments is recommended. Normal skin surrounding the spots is also to be included in measurement to eliminate the effect of non-melanin factors such as blood flow. Attach a paper strip or a color scale (e.g. CASMATCH®) as a whiteness standard before taking photographs. Save the photographs in which the spots and the surrounding normal skin are marked. Lightness and MI should desirably be

evaluated using image analysis.

2. For senile pigment freckles or ephelides smaller than the probe bore and their aggregation, evaluation based on image analysis is recommended. Attach a paper strip or a color scale (e.g. CASMATCH®) as a whiteness standard before taking photographs. Save the photographs in which the spots and the surrounding normal skin are marked. Lightness and MI should desirably be evaluated. Images are to be saved as non-compressed or low-compressed image files that can be magnified on the monitor screen as much as possible. Constant brightness and contrast lighting conditions of images is mandatory.

3-2. Parameter processing

3-2-1. L*a*b* (also applies to other color systems)

Data on the surrounding normal skin are to be documented as well as those on the spots. L* is used as a parameter. When the effect of substantial changes in facial redness (a*) may affect L*, however, it is desirable to use the difference in L* (ΔL*) between the two sites as a parameter.

3-2-2. Spectral reflection factor

Spectral reflection factors are to be converted to the color system and the melanin index (MI).

The following formula is generally used for MI conversion:

$$MI = [\log (R_{\lambda 1}) - \log (R_{\lambda 2})]^* \times 100$$

R_λ represents the reflection factor at wavelength λ. A wavelength from 670 to 720 nm should be selected for λ_1 and from 620 to 650 nm for λ_2. MI linearly correlates to the melanin quantity and is hardly affected by the redness. However, reflection factors at wavelengths of 540 to 570 nm with which the Erythema Index (EI) can be calculated should be documented in case of congestion involvement. The same formula can be used for conversion to EI; however, a wavelength from 540 to 570 nm should be selected for λ_2[1,4]. When the effect of substantial changes in facial redness (EI) may affect L*, it is desirable to use the difference in MI between the spot area and the surrounding normal skin as a parameter.

The same principle applies to EI and MI for the Erythema/Melanin Index meter.

3-2-3. RGB brightness data

Conversion of RGB brightness data to specific parameters in the image analysis should be documented. If the effect of changes in facial redness cannot be ignored when using the brightness converted to HIS system or L*a*b* system as a parameter, it is desirable to use the difference between the spot area and the surrounding normal skin. When converting brightness to an image showing MI, the formula [255 – log(*R* brightness) × 255/log (255)] may be used, provided the brightness of the image is constant (modification of the method is described in Reference 5). For the procedure used to measure spot area, the algorithm and the differentiation threshold for spot identification should be described.

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<Cosmetics Evaluation Guidelines>

Guideline for New Efficacy Claims of Sunscreen Products

Task Force Committee for Evaluation of Sunscreen Functions*

1. Introduction

In 2002, the World Health Organization (WHO) published a report[1)] recommending "voluntary restraint when sunbathing" as exposure of the skin to the sun's ultraviolet (UV) rays might cause skin cancer. In Japan, the biological effects of UV rays and necessity for UV protection were advocated with detailed information around the same time. The word "sunbathing" disappeared from the mother and child health handbook in 1999, and the Ministry of the Environment published "UV-Related Health Guidance Manual"[2)] in 2003.

Reliable technological reports on the biological damage caused by UV rays from a number of researchers were the background to the UV alert. Subjects of existing studies on the effects of UV rays on the skin could roughly be divided into the association between UV exposure and DNA damage or skin cancer, the immunosuppressive effect of UV rays, and the association between UV exposure and so-called photoaging, or epidermal and dermal damage. Many of the studies conducted in the 1990s and earlier focused on the biological effects of UVB. However, a number of recent studies reported that the effects of exposure to UVA or UVA/UVB more closely resemble those of the solar spectrum. Some of the studies showed that UVA alone could cause various types of skin damage and potentiated the effects of UVB. Many of the studies simultaneously evaluated the preventive effects of cosmetics on UV-related skin damage and reported cosmetic products with a certain level of UV protection could prevent such skin damage.

The SPF testing standard and the testing standard for UVA protection[3)] established by Japan Cosmetic Industry Association (JCIA) as the industry's voluntary standards have been widely used in the evaluation of cosmetic UV-protection in Japan. The objectives of the standards are to enable consumers to select products suitable for their individual needs for UV protection based on accurate information, to enable testing of a wide range

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of UV-protective effects including UVB and UVA protection, and to provide standards in accordance with commonly used international testing methods as much as possible. The SPF testing standard was revised in 2003 based on the International Sun Protection Factor (SPF) Test Method[4] jointly developed by the European Cosmetic, Toiletry and Perfumery Association (COLIPA), the Cosmetics, Toiletries and Fragrances Association of South Africa (CTFA/SA), and JCIA. The "UV-Related Health Guidance Manual" published by the Ministry of the Environment describes the use of cosmetics as a means of preventing UV-related skin damage and introduces the UV protection testing/labeling methods established by JCIA, reflecting the wide recognition cosmetics have received as UV protection agents.

As UV protection through the use of cosmetics now has an important role in health promotion and improvement of the quality of life (QOL) of Japanese people and the industrial testing standard has become a common basis in the developing cosmetic market, cosmetic manufacturers have been actively developing technologies for UV protective products. As a result, products with higher quality in terms of safety and usability and higher levels of UV protection have been launched in the market.

On the other hand, the efficacies of UV protective cosmetics approved by the regulatory authority so far are only "prevention of sunburn" and "prevention of spots and freckles due to sunburn" despite a number of study reports on the ability of UV protective cosmetics to prevent UV-related skin damage and improvements to the functions and quality of such cosmetics. Prevention of sunburn and associated spots/freckles is only part of the scientifically demonstrated efficacies of UV protective cosmetics. Consumers have not been accurately informed of the functions of UV protective cosmetics, and a change to the "official" efficacies has been called for. The Japanese Cosmetic Science Society (JCSS) held discussions through academic symposiums and seminars to respond to such a request; however, no specific measures were determined.

JCSS therefore decided to clarify the cosmetic functions and develop objective evaluation criteria. In 2003, the "Cosmetics Evaluation Committee," a special committee of JCSS, and subcommittees for anti-aging products, whitening products, sunscreen, and safety of functional cosmetology were established.

With the objective of developing "a guideline for new efficacy descriptions for sunscreen products," the Task Force Committee for Evaluation of Sunscreen Functions

surveyed and analyzed reliable (mostly overseas) study reports on sunscreen products' effects on the prevention of photoaging, reviewed the evaluation methods used in the studies, and discussed potential new efficacy descriptions and labeling conditions. This guideline summarizes the new efficacy description of sunscreen products that could be included in the labeling and the labeling conditions based on domestic and overseas situations, the current scientific knowledge, and internationally recognized evaluation methods identified in said survey and analysis. The guideline is subject to revision should any new scientific knowledge be obtained or new evaluation methods be developed in the future.

"Sunscreen products" in this guideline refer to any and all cosmetics (including quasi-drugs) with UV protective effects.

2. Prevention of Photoaging with Sunscreen Products

The Task Force Committee for Evaluation of Sunscreen Functions studied the existing literature on the protective effects of sunscreen products on skin damage such as photoaging. Specifically, medical study reports in English published up until 2003 were collected and reviewed based on 4 key words: skin, damage, ultraviolet, and sunscreen.

2-1. Reduction in epidermal and dermal damage due to UV exposure

Seite et al. reported that daily UV protection by use of a sunscreen product reduced skin damage based on a 6-week UV exposure experiment (irradiation of 1 MED, 5 days a week) in 12 volunteers. The study demonstrated inhibition of increase in dermal tenascin, decrease in type I procollagen, increase in skin thickness, and changes in skin surface such as coarse texture and decreased density[5]. Seite et al. also conducted a long-term (13-week) UVA irradiation experiment in human subjects and reported that use of a sunscreen product (UVA protection) eventually prevented UVA-related epidermal and dermal damage since the product was effective in the maintenance of skin moisture, skin elasticity, skin pigmentation level, and stratum corneum thickness and inhibition of tenascin expression and lysozyme deposition[6].

The UV exposure study in the three-dimensional cultured human skin model by Bernerd et al. reported that the use of a sunscreen product (SPF 7) reduced fibroblast apoptosis and changes in the granular layer and that sunscreen products with a higher level

of UVA protection reduced skin damage to a greater extent compared to products with the same SPF and lower UVA protection[7].

Rouabhia et al. reported in their study of solar simulator irradiation of engineered human skin that the use of a sunscreen product with SPF 28 significantly reduced basal cell layer damage, epidermolysis/dermolysis, morphological changes in keratinocytes, laminin decrease, and changes in basement membrane[8].

Kligman et al. reported the usefulness of a sunscreen product with SPF 15 for prevention of photoaging based on the reduced collagen damage and elastic fiber hyperplasia shown in a series of UV exposure studies in hairless mice[9-12]. In addition to prevention of photoaging, application of a sunscreen product may also prevent further UV-related damage to skin already damaged by UV exposure[11,12].

2-2. Reduction in DNA damage and skin cancer

The UV exposure study in hairless mice and the three-dimensional cultured human skin model by Gelis et al. demonstrated that the use of a sunscreen product reduced p53 expression, sunburn cells, and fibroblast apoptosis. The study reported sunscreen products with higher UVA protection reduced these phenomena more significantly and were more effective in the inhibition of skin cancer[13].

Rigel reported in his UV exposure study in human epidermis that thymine dimer production was inhibited by the use of a sunscreen product with SPF 15[14]. Liardet et al. reported the use of a sunscreen product with SPF 15 and UVA/UVB protection reduced DNA damage such as pyrimidine dimer and 8-OhdG[15]. Ling et al. reported that use of a sunscreen product with SPF 15 inhibited the thymine dimer formation[16]. Cayrol et al. studied the relation between the SPF of sunscreen products and fibroblast damage (unscheduled DNA synthesis) and reported that a higher SPF was associated with greater reduction in unscheduled DNA synthesis and that sunscreen products with an SPF under 15 were not associated with such reduction[17].

Van Praag et al. reported in their UVB exposure study in human subjects that a sunscreen product with SPF 10 was effective in the inhibition of cyclobutane pyrimidine dimer induction and prevention of DNA damage[18]. Bykov et al. also reported that a sunscreen product with SPF 10 protected the skin from cyclobutane pyrimidine dimer and production of (6-4) photoproducts but the efficacies differed depending on study

participants[19]. Arase et al. also reported that products with higher SPF prevented DNA damage (pyrimidine dimer) in fibroblasts more significantly[20].

Farmer et al. reported in their 2-year clinical study in patients with actinic hyperkeratosis that a sunscreen product with SPF 29 reduced new onset of actinic hyperkeratosis by 36%[21]. Horiki et al. reported in their UV irradiation study in mice that a sunscreen product with SPF 60 significantly delayed tumor onset and reduced the number of tumors compared with products with SPF 10[22].

Guercio-Hauer et al. reported that the daily use of a sunscreen product with SPF 15 from infancy through adolescence reduced the lifetime incidence of non-melanoma skin cancer by 78%[23]. Wulf et al. studied UV-related tumorigenesis and survival in hairless mice and reported that application of a sunscreen product delayed onset of skin cancer and prolonged survival in the UV exposed mice[24].

2-3. Daily use of sunscreen

Studies on daily sunscreen use in which "no application" days were intentionally scheduled to evaluate the sun's effects on the skin showed that "no application" of the sunscreen product caused an increase in thymine dimer formation[14], increase in sunburn cells, and a decrease in Langerhans cells[25], demonstrating the efficacy of daily sunscreen use.

The studies suggest that the daily use of sunscreen products with an SPF of at least 15 and UVA/UVB protection may prevent skin photoaging and its progression due to UV exposure.

3. Current Situation in Japan

The Japanese Pharmaceutical Affairs Law stipulates four categories: Drugs, Medical Devices, Quasi-Drugs, and Cosmetics. Sunscreen products fall into the Cosmetics category.

Labels of sunscreen products only contain the efficacy description for UV protection that the Pharmaceutical Affairs Law allows for cosmetics, specifically, "protects against sunburn" and "prevents spots and freckles caused by sunburn."

UVB and UVA protection is shown on the product label based on the Sun Protection Factor (SPF) and Protection Grade of UVA (PA) specified by the testing standard of the

Japan Cosmetic Industry Association (JCIA) [SPF testing standard (revised in 2003) and the testing standard for UVA protection] as follows[3]:

- SPF is indicated by a number up to 50 (SPF of 50 or higher is shown as SPF 50+).
- PA is shown as PA+ (PA of 2 or higher and less than 4), PA++ (PA of 4 or higher and less than 8) or PA+++ (PA of 8 or higher).

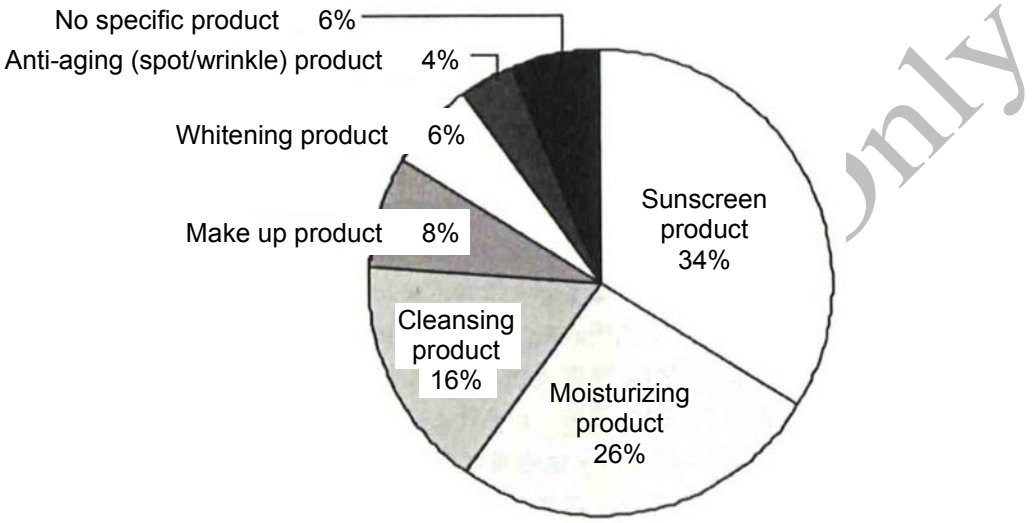

Fig. 1. Satisfactory Cosmetic Products[26]

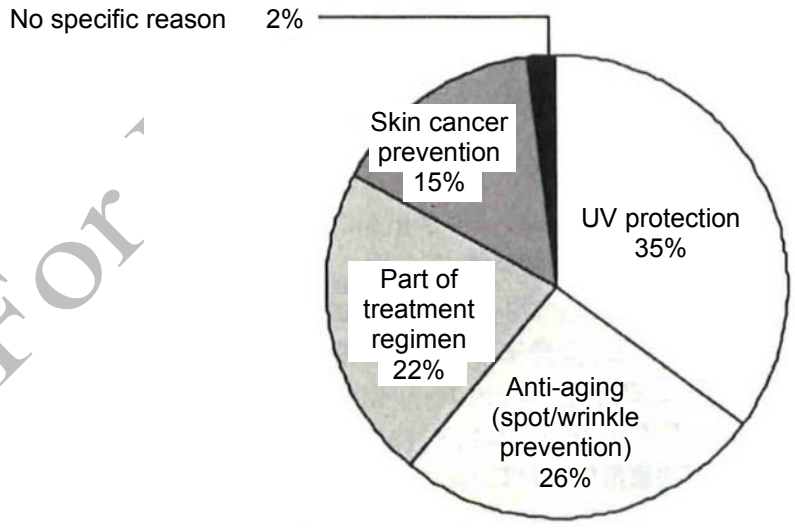

Fig. 2. Reasons for Recommending Sunscreen Products to Patients[26]

The SPF testing standard (revised in 2003) was developed based on the international SPF Test Method (in English)[4] jointly developed by JCIA, the European Cosmetic, Toiletry and Perfumery Association (COLIPA), and the Cosmetics, Toiletries and Fragrances Association of South Africa (CTFA/SA). The testing standard developed in Japan for UVA protection is the first of its kind in the world.

Labels of sunscreen products in the other major countries contain descriptions of photoaging prevention due to the raised awareness of the importance of UV protection; however, such descriptions are not allowed for sunscreen products marketed in Japan.

Expectations of Japanese dermatologists for sunscreen products are high. According to the questionnaire survey administered to 618 dermatologists by Matsunaga, the survey respondents were most satisfied with "sunscreen products" among the cosmetics available in the market. The number one "reason that I recommend sunscreen products to my patients" was "UV protection" followed by "anti-aging (prevention of spots and wrinkles)," suggesting that dermatologists' recommendation to use sunscreen products is based on their awareness of and expectation for the effectiveness of UV protection and prevention of photoaging[26].

4. Current Situation in Other Countries

Sunscreen products are categorized as either drugs (e.g. OTC drugs, therapeutic goods) or cosmetics in other major countries.

Efficacy descriptions for sunscreen products are subject to legal regulations in countries where the products are categorized as drugs. Descriptions related to prevention of photoaging are allowed in some countries if the product has the specified SPF (e.g. 15+, 30+) and UVA protection (e.g. broad spectrum sunscreen if the product is intended for UVA protection).

On the other hand, no such clear regulation is applied to sunscreen products in countries where the products are categorized as cosmetics. For example, efficacies are described on the labels at the discretion of individual manufacturers in the EU. SPF indicates that the UV protective effect of the product has been tested in accordance with the International SPF Test Method[4].

Efficacy labeling in the U.S.A, Australia, and Canada where sunscreen products became categorized as drugs (e.g. OTC drugs, therapeutic goods) as of September 2005 is described below.

4-1. United States

In the U.S, sunscreen products are sold as over-the-counter (OTC) drugs, the purchase of which does not require a doctor's prescription. However, sunscreen lotion and cream are subject to certain legal regulations for cosmetics (e.g. complete ingredient labeling).

The OTC Sunscreen Final Monograph published in May 1999 specifies label description of UV protection as follows[27]:

Two types of product efficacy descriptions may be used following "use."

- Use of the terms "sun block" and "all-day protection" is prohibited.
  - help prevent sunburn
  - higer SPF gives more sunburn protection

UV protection performance of sunscreen products is categorized into three levels and must be provided in the Principal Display Panel (PDP) under the heading "Other information."

  - minimal sunburn protection (SPF2 to under 12)
  - modrerate sunburn protection (SPF12 to under 30)
  - high saunburn protection (SPF 30 or above)

- As a description in "Sun Alert" in "Other information," provision of the following sentence is recommended but not mandatory:

"Limiting sun exposure, wearing protective clothing, and using sunscreens may reduce the risks of skin agining, skin cancer, and other harmful effects of the sun"

- According to the OTC Final Monograph published in May 1999, the following efficacy descriptions concerning UVA protection by avobenzone[26] or zinc oxide[29] proposed in the OTC Sunscreen Tentative Final Monograph may be used until the FDA makes its final determination regarding the anti-photoaging effects of sunscreen products:
  (1) Broad spectrum sunscreen
  (2) Provides (select one of the following: UVB and UVA or broad spectrum) protection
  (3) Protects from UVB and UVA (select one of the following: rays or radiation)
  (4) (Select one of the following: Absorbs, Protects, Screens, or Shields) throughout the UVA spectrum (*The word "throughout" is used for

avobenzone), within the UVA spectrum (*The word "within" is used for zinc oxide)

(5) Provides protection from the UVA rays that may contribute to skin damage and premature aging of the skin.

The FDA was requested to present its final decision on UVA-related testing methods and labeling after the publication of the OTC Sunscreen Final Monograph in May 1999. However, no new version of the OTC Sunscreen Final Monograph has been published as of September 26, 2005[30].

4-2. Activities of the Skin Cancer Foundation (U.S.)

The U.S. private organization "The Skin Cancer Foundation" awards its "Seal of Recommendation" to sunscreen products that satisfy the following criteria[31]:

- A sun protection factor (SPF) of 15 or greater
- Validation of the SPF number by testing on 20 people
- Acceptable test results for phototoxic reactions and contact irritation
- Substantiation for any claims that a sunscreen is water-, or sweat-resistant

The Seal of Recommendation is granted not only to sunscreen products but also to sunglasses, UV films for glass windows, UV umbrellas, and UV fabrics.

4-3. Australia

Sunscreen products are considered to be drugs (therapeutic goods) in Australia.

After the revision of the Therapeutic Goods Regulations in 2002[32], the Australian regulatory guidelines for OTC medicines[33] specify descriptions of UV protection as follows:

- For Broad Spectrum Sunscreen, the following description may be used:
  - can aid in the prevention of premature skin aging (or words to that effect)
- For Broad Spectrum Sunscreen with SPF 30+, the following descriptions may be used if "avoidance of long-term sun exposure" and "importance of wearing sun protective clothing, hats, and glasses" are emphasized at the same time:
  - may assist in preventing some skin cancers
  - may reduce the risk of some skin cancers
- Three testing methods (liquid method, thin-film method, and plate method) for

checking the effectiveness of Broad Spectrum Sunscreen (including UVA protection) based on UVA absorption are described. Labeling of Broad Spectrum Sunscreen is allowed if the following criteria are satisfied[34]:

- UVA (320 to 360 nm) absorption in a 8 μm-layer of the product is 10% or less Or
- UVA (320 to 360 nm) absorption in a 20 μm-layer of the product is 1% or less

4-4. Canada

Sunscreen products are considered to be drugs (therapeutic products) in Canada.

The Therapeutic Products Directorate, revised in 2002, specifies descriptions of UV protection as follows[35]:

- The following descriptions may accompany the SPF labeling:
  - sunburn protectant, sunscreen, or sunblock.
  - helps prevent, or protects, from sunburn:
  - blocks, filters or screens certain of the sun' harmful Ultraviolet or UV rays to help prevent sunburn;
  - for sun-sensitive, or fair-skinned persons, to prevent sunburn;
  - for skin where exposure to ultraviolet (or UV) light is contraindicated (only applicable for products of SPF treater than 15);
  - provides X time your natural protection against sunburn;
  - gives sunburn protection;
  - the liberal and regular use of this product over the years may help reduce the chance of premature aging of the skin;
  - UVA/UVB sunburn protection, UVA/UVB protection;
  - broad spectrum UVA/UVB protection, broad spectrum protection against UVA/UVB rays;
  - absorbs throughout the UVA/UVB spectrum to provide sunburn protection;
  - protects against UVA/UVB rays.
- The following statement may be made for Broad Spectrum Sunscreen with SPF 15 or higher:
  - The Sun may cause sunburn, premature aging of the skin and skin cancer. Avoiding the sun, wearing protective clothing and regular use of sunscreens

over the years may reduce the chance of these harmfuleffects.

5. Efficacy Description

The following efficacy description should be provided for sunscreen products with adequate UV protection:

"Daily use of the product inhibits wrinkles and spots caused by long-term UV exposure (photoaging)."

"Forgetting" to apply sunscreen, sunscreen "wear-off" due to bathing, rubbing or wiping, and use of sunscreen products with inadequate UV protection for the specific activities are potential problems in actual sunscreen use. Photoaging is caused by long-term UV exposure. In order to call attention to and raise awareness regarding these potential problems, several precautions were prepared. Depending on the intended use and the UV protection level of the product, one or a combination of following precautions should be provided together with the efficacy description. These precautions may be replaced by other phrases as long as their meanings are consistent.

"Use UV protection every day."

"Reapply every 2 to 3 hours."

"Reapply if the skin is vigorously wiped with a towel."

"Protect yourself from UV rays by also wearing hats with wide brims, using UV umbrellas, and wearing long-sleeved clothing as much as possible."

"Avoid unnecessary outings during the peak UV time (from 10:00 AM to 2:00 PM)."

6. Conditions for Efficacy Labeling

The SPF testing standard described in this guideline has been used as an international standard for a long time while the testing standard for UVA protection is Japan's original standard. Both standards must be complied with in Japan. The proposed efficacy description for sunscreen products should therefore be labeled based on these standards under the conditions described below.

6-1. SPF and PA

The proposed efficacy description may be included in the labels of sunscreen products with SPF 15 or higher and PA+ or higher if the labels indicate the SPF and PA

levels.

The requirement of SPF 15 or higher is based on the literature review mentioned earlier that concluded products with SPF 15 were expected to provide adequate daily UV protection. No scientific evidence that links PA levels and prevention of photoaging has been published so far. Despite the wide recognition of the necessity for UVA protection, existing UVA studies are limited. The requirement of PA+ or higher (PFA 2 or higher) was specified to ensure minimum UVA protection. These conditions should be reviewed and changed as necessary based on new study outcomes in the future.

SPF and PA should be tested by third-party institutions in accordance with the voluntary standard of JCIA. Evidential documents should be retained by the distributor at least while the product is in the market. The testing standards for SPF and PA, especially the SPF testing standard, have been updated in line with technological advances. Tests should be conducted in accordance with the latest standard after an update is released. JCIA's SPF testing standard, revised in 2003[3)], is used as of October 2006; however, use of the revised version is scheduled for 2006.

6-2. Target products

The proposed efficacy description may be used for any and all sunscreen products with the UV protection specified above. However, products not intended for skin application such as hair products and products for eyelashes are not included, even if they have adequate UV protection.

Many of the so-called point make-up products (e.g. lip color, eye shadow, eye liner, blush) are intended for "beautifying, increasing attractiveness, and changing looks" according to the definition of cosmetics provided in the Pharmaceutical Affairs Law, and are not intended to provide UV protection. Therefore, no point make-up product that satisfies the criteria for UV protection mentioned earlier exists at the moment. However, point make-up products with adequate UV protection may be developed and sold in the future. In that case, the proposed efficacy description may also be used for such products. Since only a very limited skin area will be protected from UV rays by point make-up products, combined use with other products that can be applied to wide areas will be required in order to prevent photoaging. Certain matters need to be considered when preparing labels for point make-up products, such as providing a precaution, to avoid

consumer misunderstanding.

The proposed efficacy description is intended for sunscreen products that absorb, diffuse or block UV rays on the skin and thus give UV protection. Should any new product with a different mechanism of UV protection from those of current sunscreen products, such as a product that penetrates the epidermis and stays in the dermis to exert its effect, be launched in the market in the future, the efficacy description and labeling for such a product and relevant safety issues will be discussed and determined separately.

6-3. Safety considerations

It is recommended to adequately evaluate the safety of sunscreen products with the proposed efficacy labeling in accordance with the Guideline for Evaluation of Safety of Functional Cosmetology developed by the Task Force Committee for Evaluation of Safety.

7. Proposal for Efficacy Labeling

Mere labeling of the proposed efficacy description by manufacturers will not be sufficient to help consumers understand the efficacy description prepared by the Task Force Committee for Evaluation of Sunscreen Functions and use the products effectively. It will be necessary to accurately inform consumers of the importance of preventing photoaging and how to prevent photoaging appropriately in cooperation with medical professionals such as dermatologists.

Products should satisfy the aforementioned conditions in order to include the proposed efficacy description in their labels. In addition, SPF and PA test reports that serve as evidence of the product's efficacy should be reviewed by an independent third-party institution to ensure and certify that the product satisfies the required conditions.

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<Cosmetics Evaluation Guidelines>

Guideline for Evaluation of Safety of Functional Cosmetology

Task Force Committee for Evaluation of Safety*

1. Introduction

In safety assurance of quasi-drugs and cosmetics, a variety of factors such as safety of individual ingredients contained in the product, product usage, and intended application site should be considered. This chapter describes the basic concept of safety assurance of novel and existing ingredients (hereafter, "functional ingredients") to be evaluated based on the guidelines for evaluation of anti-aging products, whitening products, and sunscreen products and provides a guideline for human studies on products containing functional ingredients in which a final product safety evaluation is to be made.

2. Safety Evaluation of Functional Ingredients

2-1. Novel ingredients

2-1-1. Safety evaluation overview

Proven safety as a cosmetic ingredient is the prerequisite for a novel functional ingredient to be further evaluated for its safety. Novel functional ingredients should basically be tested for single-dose toxicity, primary skin irritation, repeated skin irritation, phototoxicity, conjunctival irritation, contact sensitization, photosensitization, genotoxicity (bacterial reverse mutation, chromosomal aberration in cultured mammalian cells, micronucleus), and be subjected to a human patch test as specified in the "Guideline for Cosmetic Safety Evaluation 2001"[1]. Since effects/efficacies of functional ingredients are more clearly defined and claimed compared to traditional quasi-drugs and cosmetics, they need to be tested for their functions and functional characteristics or action mechanisms (e.g. modification of specific enzyme activity) and evaluated in human studies in addition to said basic studies for cosmetic ingredients (Fig. 1).

2-1-2. Specific tests for functional ingredients

Specific test items for functional ingredients include transdermal absorption, multiple dose toxicity, reproductive toxicity, carcinogenicity, and metabolism/distribution/elimination. After the basic tests for cosmetic ingredients,

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transdermal absorption is tested. Absence of transdermal absorption means that the ingredient functions on the skin surface, and further safety evaluation is unnecessary. A functional ingredient with confirmed transdermal absorption may be transferred into the blood and cause systemic toxicity. Such an ingredient should be tested for multiple dose toxicity, reproductive toxicity, and carcinogenicity as well as other items in accordance with the toxicity profile. A quantitative risk assessment should eventually be made by calculating the safety ratio based on the exposure in actual use and the no-observed-adverse-effect level (NOAEL) obtained in said tests. In addition to transdermal absorption, metabolism/distribution/elimination of the ingredient should be evaluated as necessary. Safety evaluation of the metabolite should be considered if the safety of the metabolite is relevant.

To evaluate the functional characteristic or the action mechanism, an optimal test system must be used to locally and systemically evaluate the biologic substances involved in the action mechanism and the effect of the ingredient on physiological functions. The OECD (Organisation for Economic Co-operation and Development) Guideline[2], COLIPA (European Cosmetic, Toiletry and Perfumery Association) Guideline, SCCNFP (Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers) Guidance[3], and ICH (International Conference on Harmonization) Guideline[4] could be used as references when preparing protocols for the tests mentioned above. Needless to say, however, testing methods provided in these guidelines should not necessarily be used in their given forms. Optimal testing conditions for appropriate evaluation should be determined based on the physical properties of the ingredient, available information on comparable ingredients, and pilot test results (Fig. 2).

Filing of applications for marketing approval or request for listing in the Positive List with Ministry of Health, Labour and Welfare is required for novel functional ingredients with anti-aging or whitening functions (active ingredients of quasi-drugs) and those with sunscreen functions (UV absorbers). Test items required for novel ingredients with said anti-aging functions or whitening functions include all items listed in "Attachment: Data to be Attached to Quasi-Drug Application" concerning novel quasi-drugs (Application Category 1) in the "Cosmetics/Quasi-Drugs Marketing Guidebook 2006"[5], and test items required for novel ingredients with sunscreen functions include all items listed in the "Positive Listing Guideline" in said Guidebook.

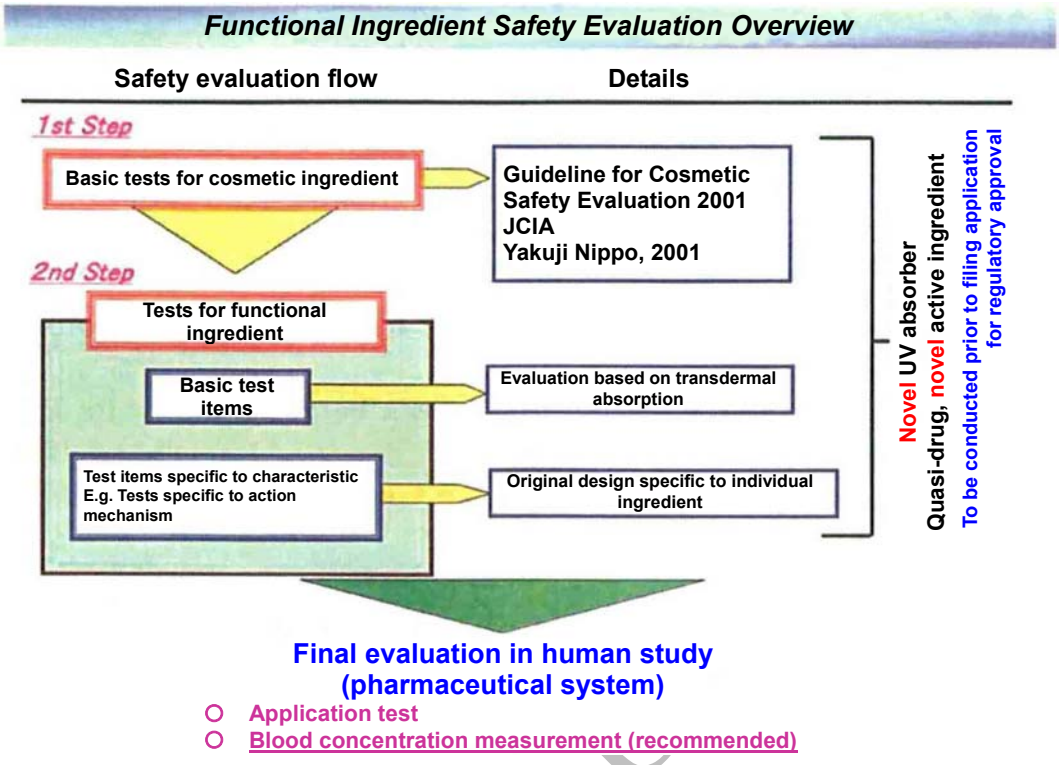

Fig. 1. Safety of Functional Ingredient

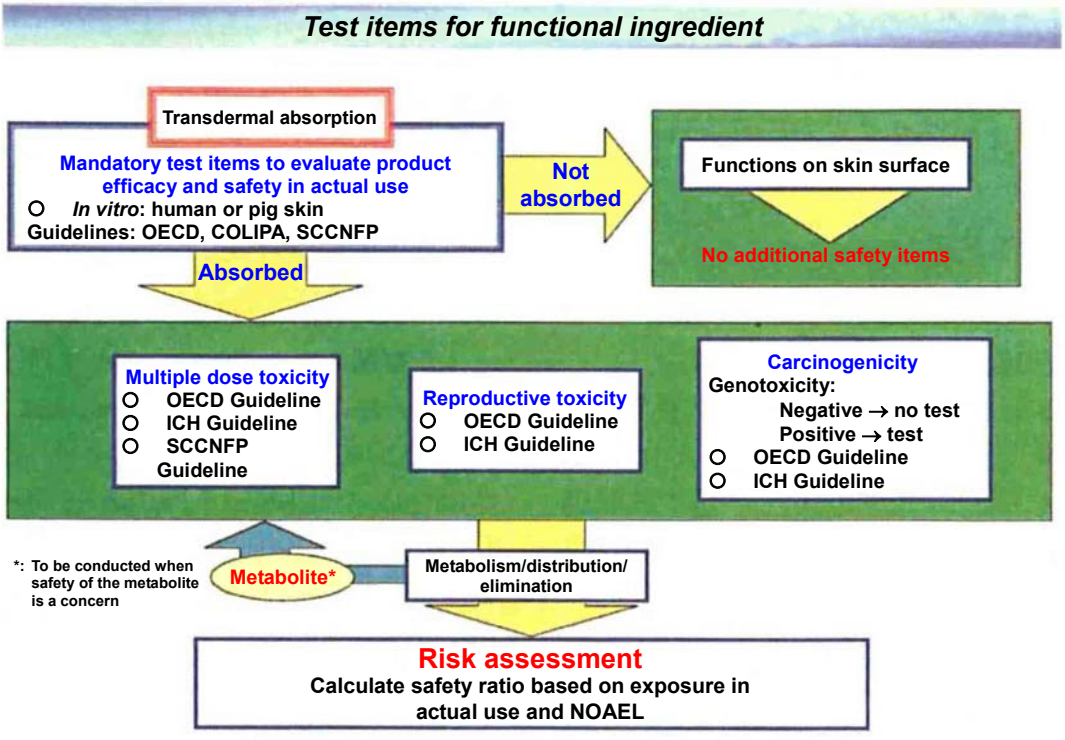

Fig. 2. Test Items for Functional Ingredient

2-2. Existing ingredients

Since safety of existing functional ingredients have been already proven through studies on their raw materials and products they are contained in as well as through formulation experience, no human study or other supplemental study is required. However, safety of products containing existing ingredients with additional or enhanced anti-aging or whitening functions based on their intentionally increased transdermal absorption compared with other currently available products needs to be reevaluated in terms of content, usage, and application site by referring to the results of safety studies on the raw materials. Studies in accordance with the Guideline for Application Study in Human Subjects described later will also be necessary (Tables 1 and 2).

2-3. Application study in human subjects

Products containing novel functional ingredients or existing ingredients with additional or enhanced anti-aging or whitening functions based on their intentionally increased transdermal absorption compared with other currently available products should be subject to pharmacokinetic tests in accordance with the guideline described later to ensure product safety in actual use in human subjects after being evaluated in the tests described in Section 1. Such products may be tested for safety evaluation alone by omitting evaluation of anti-aging, whitening or sunscreen functions or may be tested for both safety and functional evaluations.

In application studies in human subjects, safety evaluation based on the blood concentration of the functional ingredient is recommended since such studies will be conducted for final safety evaluation of the ingredient and more thorough safety assurance is required in functional ingredients that claim to have potent effects on human skin.

3. Guideline for Application Study in Human Subjects

3-1. Objective

Products containing novel ingredients with anti-aging, whitening or sunscreen functions or containing existing ingredients with intentionally increased transdermal absorption compared with other currently available products are to be tested for safety in actual use. Application studies in human subjects are to be conducted for final safety evaluation of novel ingredients. The guideline provides only what is required for such

studies regardless of types of functional ingredients, for example, sample size and duration of trial application. For other study-related matters, refer to the guideline for regular cosmetic studies in human subjects.

3-2. Study implementation

In principle, the study sponsor should contract the study to a dermatological specialist certified by the Japanese Dermatological Association (hereafter, "dermatological specialist").

Sub-investigator(s) who conduct studies under the supervision of the dermatological specialist may be appointed as necessary.

Table 1. Safety Assurance for Ingredients with Anti-Aging or Whitening Function

Type of ingredient	Safety assurance		
	Raw material	Product	
		No intentional consideration of transdermal absorption in prescription design	Product designed by intentionally adding or enhancing function based on increased transdermal absorption
Existing ingredient	Confirmed (including post-marketing experience)	Confirmed (including post-marketing experience)	**To be tested in human study**
Novel ingredient	To be tested	**To be tested in human study**	

Table 2. Safety Assurance for Ingredients with Sunscreen Function

Type of ingredient	Safety assurance		
	Raw material	Product	
		No intentional consideration of transdermal absorption in prescription design	Product designed by intentionally adding or enhancing function based on increased transdermal absorption
Existing ingredient	Confirmed (including post-marketing experience)	Confirmed (including post-marketing experience)	**To be tested in human study**
Novel ingredient	To be tested	**To be tested in human study**	

3-3. Ethics

Studies should be conducted in compliance with "Ethical Guideline for Clinical Research (MHLW Announcement No. 255, 2003)" dated July 30, 2003. Review and

approval of the ethical review board and voluntary written consent of study participants are mandatory. Information on study participants should be stored and managed carefully in light of protection of personal information.

3-4. Study participants and exclusion criteria

3-4-1. Study participants

Healthy volunteers who understand the objective of the study and are willing to cooperate are to be enrolled.

3-4-2. Exclusion criteria

A. Persons with skin abnormalities such as inflammation and eczema at the intended application site
B. Persons whose participation in the study is determined inappropriate by the dermatological specialist
C. Eligibility of pregnant or possibly pregnant women is to be determined by the dermatological specialist.

3-5. Sample size

Necessary and adequate number of participants should be enrolled in accordance with the novelty and characteristic of the ingredient as well as with the characteristics of the product.

3-6. Duration and frequency of product application

Minimum duration and frequency of product application need to be ensured in the study to allow the product to show its claimed function. Duration of product application should be at least 1 month.

Frequency of daily application should be the same as in actual use.

3-7. Application site

The product should be applied to the same area as in actual use.

3-8. Control sample

Control sample(s) is to be used as necessary.

3-9. Evaluation method

A. The double-blind method should be used when two or more study groups are established.

B. Questionnaire: To be distributed before the study starts and collected after the trial application is completed. The following questionnaire items are to be included:

- ○ Pre-study: cosmetic products regularly used, current skin condition, skin type, skin sensitivity, past skin problems with cosmetics/quasi-drugs/drugs, allergies, atopic disposition
- ○ During study: daily product use, skin abnormality (symptoms and signs)

C. Observation or interview:

<Timing of observation/interview>

Participants are to be observed/interviewed before and after product application. Observation/interview is to be scheduled as necessary during the trial application period.

- ○ The participant should be withdrawn from the study should any of the following occur during the study. Necessary observations should be conducted at the time of withdrawal whenever possible for safety (or efficacy) evaluation. Any abnormality seen in the application site should be followed until the symptom disappears in principle, and the participant should be referred to the dermatological specialist as necessary.
  - Participant requests his/her withdrawal.
  - Continuation of the study is determined to be difficult due to occurrence of adverse events.
  - Continuous use of the test product becomes difficult due to an accident or illness during the study.
  - Withdrawal of the participant is otherwise determined necessary by the dermatological specialist.

<Observer/interviewer>

- ○ Pre- and post-trial application: dermatological specialist
- ○ During trial application: dermatological specialist or sub-investigator

<Observation items>

- ○ Skin findings:

Symptoms: itchiness, irritation, etc.

Signs: erythema, desquamation, papule, skin pigmentation, depigmentation, capillary dilatation, swelling, etc.

○ Others

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