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Whitening

Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims

Task Force Committee for Evaluation of Whitening Function

1. Introduction

Dark spots and freckles are frequently cited as pigmentation and skin-color problems in surveys on skin trouble. Reflecting this concern about their skin, consumers have high expectations of cosmetic products that promise a whitening effect, and the market for such products is very large.

Under Japan's Pharmaceutical Affairs Law, whitening cosmetics are classified as quasi-drug products and are allowed to make only two possible efficacy claims: "prevents pigmented spots and freckles due to sun exposure," or "prevents pigmented spots and freckles by inhibiting melanin formation."[1] Only preventive effects can be claimed, and only those two. However, consumers expect more than mere prevention; they also want whitening cosmetics that will improve pigmented spots and freckles that have already formed. The Task Force Committee for Evaluation of Whitening Function (hereinafter the "Committee"), which is part of the Cosmetic Science Society's Committee for Studying Evaluation Methods for Cosmetic Functions, conducted a survey that found that consumers wanted whitening products that would facilitate the "disappearance of pigmented spots and freckles" and the "lightening of pigmented spots and freckles."[2]

With the tremendous advances that have been made in science and technology, we have accumulated much knowledge concerning the mechanism for the formation of melanin and the control of melanin synthesis. Tremendous progress has also been made in evaluation technologies pertaining to the skin, including those for evaluating the condition of the skin surface and those for measuring skin color. Because of these advances, it is getting easier to analyze the efficacy claims of whitening cosmetics. In fact, a number of trials have reported on their efforts to evaluate the ability of such cosmetics to improve pigmentation.[3)–26)]

Against this background, the Committee carried out a project to study the drafting of Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims, as its contribution to the realization of evidence-based claims by cosmetics in this field. Because it is important to create proper methods for obtaining the evidence needed to effectively evaluate new indications, the goal of the Committee was that the guidelines and their content should ensure that testing is conducted in an appropriate manner. This was achieved through literature and questionnaire surveys. The Committee was able to make a far-ranging study of the selection of subjects, standards for judging efficacy, and various other aspects, and to determine the individual items of the guidelines from the results. At the end of this report, we discuss the Committee's proposed efficacy claim.

Of course, as we continue to see tremendous advances in science and technology, some aspects of these guidelines may no longer be appropriate in the future. In such cases, it will be necessary to make revisions. We would also like to mention that the purpose of these guidelines is to provide basic guidance on evaluation procedures. Therefore, it will be necessary to draw up a protocol of detailed procedures for each type of testing that is conducted.

2. Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims

2–1. Qualified Pigmentation Symptoms and Subjects for Testing

Subjects are healthy women and men having superficial pigmentation symptoms (chloasma, lentigo senilis, ephelides, post-inflammation pigmentation (including sunburn), etc.). Those having Ota's nevus and other serious pigmentation symptoms are excluded as subjects.

Subjects are excluded under the following circum-

stances:

(1) Those with a past history of allergic reaction to cosmetics
(2) Those undergoing hormone replacement therapy
(3) Women who are pregnant or breast feeding
(4) Those who have undergone beauty therapy that could affect the testing area
(5) Others whose participation is deemed inappropriate by a doctor

2–2. Trials and Testing Facility Requirements

Trials are carried out under the supervision of a controller according to a double-blind design. It should be possible for visual, photographic, and measuring instrument evaluations to be carried out at the testing location under constant conditions (with particular attention paid to lighting). If the trial is conducted at several facilities, it must be ascertained beforehand that no inter-facility or inter-tester deviations will arise.

2–3. Test Subjects and the Application of Tested Samples

In trials, we examine the differences between subjects in a group that uses a preparation containing the active ingredient and subjects in a group that uses a placebo (cosmetic base). (If pigmentation is symmetrical on the left and right sides of a particular subject's face, an evaluation may be carried out on both halves of the same face.) Subjects should be randomly assigned to the groups in order to ensure that there are no clear biases between the groups in terms of age distribution, degree of pigmentation, or other factors.

"Apply an appropriate amount in a normal manner" should be the general usage instruction. A guidance of usage should be prepared before beginning the trial, and then the test should be carried out. Records of the formula, manufacturing method, and date of manufacture should be kept for test samples so that follow-up investigations can be conducted as required.

2–4. Stipulations Concerning Concomitant Use of Other Products, Medicines, Etc.

During the period of the trial, the use of other whitening products and topical adrenocortical hormone preparations should be avoided. The use of oral medicines such as vitamin C preparations, vitamin EC preparations, SH preparations, tranexamic acid preparations, and contraceptive agents should also be avoided. Details of any concomitant drugs, cosmetics, or other products should be entered on case cards.

Subjects should be instructed to avoid excessive exposure to UV radiation during the period of the trial. The use of other skin care cosmetics should generally be avoided but if such products have to be used they should not contain a whitening ingredient and the same products should be used throughout the trial.

2–5. Period of the Trial

The period of the trial should be set to allow an adequate amount of time for evaluating the whitening effect (at least one month).

2–6. Number of Subjects

With reference to the results of preliminary testing and other data, the number of subjects should be determined so that sufficient data for demonstrating an effect by means of statistical analysis are produced.

2–7. Evaluation and Measurement Procedures

2–7–1. Evaluation items

- Visual and photographic evaluations of the area should be made prior to the start of the trial and at the end of the trial.
- Instrument measurements of the area should be made prior to the start of the trial and at the end of the trial.
- Evaluations should be made mid-way through the trial if necessary.

2–7–2. Measurement conditions

- Measurements should be made in a room that provides an environment with constant conditions (temperature, humidity, and lighting), and those conditions should not change throughout the duration of the trial.
- In order to avoid the influence of makeup or facial care products on the measurements, the face should be washed beforehand.
- Measurements should be taken after the subject has had about 15 minutes to acclimatize to the measurement room.
- Each time measurements are taken, the position and orientation of the body should be the same as at the start of the trial.
- Measurements should be made at the same time of day each time as far as it is possible to do so.

2–7–3. Procedure for taking photographs

- At the time of each evaluation, the conditions under which photographs of the pigmented areas are taken should be the same as they were at the start of the trial.
- To avoid error, all necessary adjustments of magnification, camera angle, framing, and other matters should be made with reference to the photographs taken at the start of the trial.
- For the purposes of color correction and scale correction for the image, a photo scale and color chart (e.g. CASMATCH®) are attached in the vicinity of the observation area so that they are seen but do not interfere with evaluation.

2–7–4. Procedures for instrument measurements

Refer to Guidance for Pigmentation Measurements (supplement to this section).

2–7–5. Evaluation of pigmentation

Refer to Guidance for Pigmentation Measurements.

2–7–5–1. Visual evaluation

An expert dermatologist or a doctor with the equivalent medical skill should conduct the evaluation; or this may be done by a Trained Expert (researcher with expert knowledge of pigmentation) under the supervision of such a doctor. Evaluation is made in accordance with the following procedures.

(A skin color chart may be used to aid the visual evaluation.)

Evaluation

- Comparison of skin before the trial and after the trial

A visual evaluation is made at the end of the trial, or mid-way through the trial, by comparing photographs taken prior to the start of the trial, and one of five grades assigned: Significantly improved, Improved, Slightly improved, No change, or Worsened.

- Comparison of skin on two halves of the same face

The difference between the two halves is evaluated and given one of three grades: Significant difference, Slight difference, or No difference.

2–7–5–2. Photographic evaluation

An expert dermatologist or a doctor with the equivalent medical skill should conduct the evaluation; or this may be done by a Trained Expert (researcher with expert knowledge of pigmentation) under the supervision of such a doctor.

- Comparison of skin before the trial and after the trial

Photographs taken prior to the start of the trial and at the end of the trial, or mid-way through the trial, are compared, and one of five grades is assigned: Significantly improved, Improved, Slightly improved, No change, or Worsened.

- Comparison of skin on two halves of the same face

The difference between the photographs of the two halves is evaluated and given one of three grades: Significant difference, Slight difference, or No difference.

2–7–5–3. Instrument Evaluation

The difference between skin at the start of the trial and at each measurement is evaluated using a reflectance spectrophotometer (or equivalent optical instrument) or a digital image processing procedure. In the case of using both halves of the same subject's face, the difference between the corresponding areas is evaluated. All measurements must be made using the identical instruments under the same measurement conditions. Even if the parameters are identical, measurement data made by other instruments should not be used for comparisons.

2–8. Adverse Events and Reactions

Adverse events are defined as various undesirable effects occurring during the period of the trial for which a causal relationship with the test sample cannot be established. Adverse reactions are defined as various undesirable manifestations occurring after a subject starts to use the test sample for which a causal relationship with the sample cannot be ruled out and there is a reasonable possibility that the manifestations were caused by it.

In either case, a report describing the details of the onset and subsequent course of the undesirable effects, their degree of seriousness, and whether or not any measures were taken, the details of the measures taken, and the outcome of treatment should be made, and the doctors supervising the test should make a judgment about whether there is a causal relationship with the test sample or not.

2–9. Subject Questionnaires

Have subjects fill out questionnaires to check for problems with the use of samples and to ascertain usage and efficacy.

2–10. Efficacy Analysis

For all evaluation items, make a comparison, using appropriate statistical methods, between the group treated with the preparation containing the active ingredient and the group treated with the placebo (cosmetic base). In the following cases, data from subjects should be omitted from the analysis.

(1) Very infrequent application or other improper use of the product.
(2) When adverse events or reactions occurring during the trial make continued participation impossible.
(3) When there is concern about the reliability of data, for example in the case where medications are being taken during the trial.

Efficacy is analyzed after eliminating data from subjects coming under the above categories and a safety analysis has been carried out for all subjects who used the test sample.

2–11. Overall Judgment of Efficacy

A product is judged to have efficacy if, as a result of the visual or photographic evaluations, there is a significant improvement in pigmentation ($p<0.05$) in the group treated with the preparation containing the active ingredient as compared with the group treated with the placebo (cosmetic base) and if the instrument measurements are not in conflict with the results of the visual or photographic evaluations.

2–12. Ethical Guidelines

Ethical considerations should be in accordance with the Ethical Guidelines for Clinical Research (Ministry of Health, Labour and Welfare Notification No. 225, 2003), dated 30 July 2003. It is necessary for testing to be approved by an ethics committee, and the informed written consent of subjects must be obtained. In order to protect personal information, adequate care must be taken in its filing and management.

3. Summing Up

The Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims establish the basic conditions for evaluating such claims. In drawing them up, the Committee studied proposed new efficacy claims to clarify its ideas on this subject. The two current efficacy claims allowed for whitening cosmetics are: "prevents pigmented spots and freckles due to sun exposure" or "prevents pigmented spots and freckles by inhibiting melanin formation." However, various proposals have been made for new indications, with the focus on such words as "alleviate" and "improve." The common focus of the Committee members in studying the various proposals for efficacy claims was to find an appropriate description of the effects of quasi-drug products. In the end, this description was chosen: "moderately improves pigmentation spots and freckles."

The thinking behind adopting the above as our proposed efficacy claim was that we wanted one that signifies the notion of improvement, because the testing in the Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims is based on evaluating improvements in pigmentation. However, it also stems from the desire of the Committee to inform consumers in an easy-to-understand manner that quasi-drug whitening cosmetics alleviate pigmentation moderately, rather than acting like pharmaceutical products. The above represents the Committee's current thinking with regard to new efficacy statements by quasi-drug whitening products, and we will continue studying this topic in the future in order to devise additional efficacy claims for them.

As the Guidelines for Evaluation of Quasi-Drug Whitening Products for New Efficacy Claims only establish basic tests for evaluation purposes, it will be essential to draw up proper protocols based on a full examination of the testing requirements and conduct a precise analysis of the results in order to obtain the evidence needed for new efficacy claims.

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Guidance for Pigmentation Measurements

1. Introduction

This guidance was established to achieve higher accuracy in the instrumental measurement of pigmentation.

2. Basic Items Concerning Instrument Measurements

The difference between skin at the start of the trial and at the time of each measurement is evaluated using a reflectance spectrophotometer (or equivalent optical instrument) or a digital image processing procedure. In situations where you are using both halves of the same subject's face, the difference between the corresponding areas is evaluated. All measurements must be made using the identical instruments under the same measurement conditions. Even if the parameters are identical, measurement data made by other instruments should not be used for comparisons.

Typical measuring instruments

1) Reflectance spectrophotometer
2) Tristimulus colorimeter

3) Erythema and melanin index meter or narrow-band spectrophotometer
4) Skin image analysis system

3. Supplementary Items in Instrumental Measurement

In order to improve the objectivity of measurements, concrete examples in measurement procedures and data processing are shown below. However, these conditions and procedures of instrumental measurement are not absolutely required.

3–1. Measurement Procedures

1. For melasma or large lentigo senilis, it is recommended to measure using spectral reflection factor, color (L*a*b*, etc), or melanin index (MI) with the contact-type instruments. In order to avoid the influence of non-melanin-related factors like blood flow, measurements are made for adjacent normal skin areas as well as the pigmented area. In addition, it is preferable to take images with a strip of paper as the white standard or a color chart (e.g. CASMATCH®) and save them. Furthermore, it is preferable to record the measured area of pigmentation and the surrounding normal skin, and also to evaluate brightness and MI by means of image analysis.
2. For small lentigo seniles and ephilides that are smaller than the aperture of the probe of contact-type instruments, it is recommended to measure using image analysis in order to evaluate accurately. In such cases, it is preferable to take images with a strip of paper as the white standard or a color chart (e.g. CASMATCH®) and save them. It is preferable to record the measured area of pigmentation and the surrounding normal skin, and also to evaluate brightness and MI. As far as possible, images should be saved as uncompressed or low compression data in case they may be expanded on the screen. However, it is required that the brightness of images remains constant.

3–2. Processing of Parameters

3–2–1. L*a*b* (Same for other color systems)

It is necessary to record the values not only of the pigmented area but also of the surrounding normal skin as well. L* is taken as the basic indicator, but in the case where facial redness (a*) changes greatly and its effect on L* cannot be ignored, it is preferable to consider the difference of L* between two locations (ΔL*) as the parameter.

3–2–2. Spectral reflection factor

The spectral reflection factor is used not only for color system conversions but also for melanin index (MI) conversions.

The normal formula for converting to MI is:

$$MI=[\log(R_{\lambda_1})-\log(R_{\lambda_2})]^*\times 100$$

R_λ stands for the spectral reflection factor for wavelength λ.

λ_1 is selected in the range 670–720 nm and λ_2 in the range 620–650 nm.[1)–3)] The MI is linearly correlated with the melanin amount and is not readily affected by redness. However, it is preferable to record the spectral reflection factor in the range 540–570 nm in order to calculate the erythema index (EI) in preparation for cases of blood stasis influence. Though the same formula is used for conversion into EI, λ_2 is selected in the range 540–570 nm.[1),4)] In the case of a great change in facial redness (EI) whose effect on MI cannot be ignored, it is preferable to consider the difference of MI in the pigmented area and the surrounding normal skin area as the parameter.

EI and MI in the erythema and melanin index meter are the same principles.

3–2–3. RGB brightness data

When the data of the RGB brightness value is converted into a specific parameter using the image analysis procedure, it is necessary to describe it clearly. In the case of using brightness values as a pigmentation indicator converting the RGB brightness value into the HSI, L*a*b*, and other color systems, and in the case of changes in facial redness that cannot be ignored, it is preferable to consider the difference of the value between the pigmented area and the surrounding normal skin area as the parameter. If image brightness is constant, it is possible to convert it into images showing the MI by the formula 255-log (R brightness)×255/log (255) (refer to the modified procedure in Reference 5). In the case of systems that measure pigmented area, an algorithm and a threshold value for isolating pigmentation should be clearly described.

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