Provisional Translation
From Japanese Original

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To: Directors of Prefectural Health Departments (Bureaus)

Director, Pharmaceutical Evaluation Division,
Pharmaceutical Safety and Environmental Health Bureau,
Ministry of Health, Labour and Welfare
(Official seal omitted)

Clinical Evaluation Guidelines for Quasi-drugs

The scope, etc. of data to be attached to the application for marketing approval of quasi-drugs are currently handled in accordance with the "Application for Approval of Quasi-drugs" (PFSB Notification No. 1121-7 by the Director-General of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated November 21, 2014).

With regard to data on clinical evaluation among "data on safety" and "data on indications" which are required to be attached at the time of application for marketing approval of quasi-drugs, points to consider, etc. for preparation have been summarized as shown in the Appendix. Therefore, we request that you inform related businesses placed under your administration of these matters.

Appendix

Clinical Evaluation Guidelines for Quasi-drugs

1. Purpose

These guidelines show points to consider, etc. when preparing data on clinical evaluation among "data on safety" and "data on indications," which are required to be attached at the time of application for marketing approval of quasi-drugs (hereinafter referred to as "approval application"). The guidelines indicate matters to be considered in the evaluation of efficacy and safety in the development stage of quasi-drugs that are used repeatedly for the face, whole body skin, lips, etc. (hereinafter referred to as "skin, etc.") and their active ingredients. For other quasi-drugs, their active ingredients, and excipients of quasi drugs, necessary evaluation shall be performed by referring to these guidelines.

These guidelines summarize the basic concepts based on the current scientific knowledge and should be reviewed according to academic progress. It is not necessarily required to adhere to the methods shown here if they are based on rationales reflecting the latest scientific knowledge.

2. Concept of development

Newly developed quasi-drugs, like new drugs, are widely used by many people for the first time after marketing, but unlike drugs, they are widely used by general consumers without limiting the target users. Since human use experience is limited in the development stage, the efficacy, and safety in particular, should be carefully examined by collecting and analyzing information from various perspectives in addition to appropriate evaluation.

3. Points to consider in conducting human studies

Before conducting a human study, it is necessary to conduct a thorough basic study on the efficacy and safety of the formulation of the product and the concentration in the formulation examined and to collect publicly known information, etc. through literature, etc. When considering the design of a human study, careful consideration should be given to the situation of actual use, data on physicochemical properties and safety, and other related information. In particular, close attention should be paid to any expected changes such as enhanced toxicity or efficacy due to the formulation of the product or the concentration in the formulation. In addition, adequate efforts should be made to ensure reliability based on the spirit of ICH-GCP.[1]

Studies in humans shall be conducted in accordance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice No. 3 of the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, dated December 22, 2014)." Review and approval by the Ethical Review Board and acquisition of written consent based on the participant's free will are essential.

(1) Human patch test

A human patch test is a powerful method to identify the cause of allergic contact dermatitis in products applied to the skin, etc. and to predict the irritancy during repeated use because of its high reproducibility as an evaluation method of primary skin irritancy caused by ingredients and products. When skin irritancy of quasi-drugs is to be evaluated, it is necessary to conduct tests appropriately with the test

[1] International Conference on Harmonization (ICH)-Good Clinical Practice (GCP)

conditions specified under the guidance of a dermatologist certified by the Japanese Dermatological Association (hereinafter referred to as "dermatologist") and evaluate irritancy appropriately based on the results obtained. Test conditions, evaluation methods, etc. shown in Table 1 can be used as reference information.

Table 1 Test conditions and evaluation methods for single irritancy evaluation by a human patch test

Target	≥40 Japanese participants
Dose concentration	In principle, patch tests using products and raw materials should be performed in several stages including the concentration at the time of actual use to confirm a sufficient safety margin. Higher concentrations than that at the time of actual use should be included if there is no ethical problem.
Negative control	Usually, solvent or physiological saline is used. Since distilled water may cause skin reactions due to osmotic pressure, it is undesirable to use distilled water as a negative control in skin irritancy evaluations. When the skin irritancy reaction of a raw material diluted with distilled water is to be assessed, distilled water may be used as a vehicle control.
Application site	Usually, closed patches should be applied to a site with a normal appearance on the upper back (paravertebral region excluding the midline region).
Observation/ evaluation	• In principle, the patch test unit should be removed 24 or 48 hours after application, the first observation should be performed usually 2 hours after removal, waiting for the disappearance of transient erythema due to removal, and the continuous irritation reaction should be observed 24 and 48 hours after removal. Assessment should be performed 72 hours and thereafter depending on the conditions of skin reactions to examine the presence or absence of allergic reactions. • Assessment should be performed according to the Japanese criteria[Note)] or a similar method. • The severity of erythema, edema, etc. should be assessed and evaluated by a dermatologist. • On each observation day, the condition of the application site of the participant should be recorded by photography, and evaluation should also be performed using photos.

Note) The assessment criteria are based on the following 6-grade criteria.

Japanese criteria	Reaction
-	No reaction
±	Mild erythema
+	Erythema
++	Erythema + edema, papule
+++	Erythema + edema + papule + vesicle
++++	Large blister

Appropriate test conditions should be established in consideration of the safety of the substance based on physicochemical properties or results of nonclinical studies, etc. It is appropriate that the participants refrain from bathing, sports, and working that causes a lot of sweating while the patches are applied. If a positive finding is observed, it should be monitored until the finding resolves, and the number of days until resolution, outcome, etc. should be documented.

The test should be performed with appropriate procedures in consideration of the characteristics and method of use of the product. For a volatile product, an open test should be performed by directly applying it to the site (application to the same site for 5 to 7 consecutive days at the normal use concentration), or the product should be applied to the patch test unit, leave it to sufficiently volatize, and then the unit should be applied to the site. For a permanent waving agent or hair coloring agent, an open test should be performed by directly applying it to the site. For a cleaning agent (body soaps, shampoos, etc.), several concentrations, mainly 1% aqueous solution, should be selected in consideration of the method of use and applied to the patch test unit to be applied to the site. Other products should be directly applied to the patch test unit to be applied to the site.

(2) Long-term human administration (safety) study

The objective of a long-term human administration (safety) study is, in principle, to evaluate the safety of long-term administration by the actual method of use of products that meet all of the following criteria [1] to [3].

[1] Quasi-drugs with new active ingredients

[2] Products to be applied to the skin, etc.

[3] Products to be used repeatedly on a daily basis

Even in the case of a quasi-drug containing an approved active ingredient, if multiple ingredients expected to have the same effect are newly combined, if a new indication is added, or if a product expected to have a superior effect, such as enhancing transdermal absorption, etc., is developed, a long-term human administration (safety) study should be conducted as necessary.

When planning an appropriate clinical study, consultation with a dermatologist and involvement of a dermatologist in the evaluation during the study should enable appropriate evaluation, including evaluation of adverse events. The study design shown in Table 2 below can be used as a reference.

Table 2Long-term human administration (safety) study

Study period and number of participants	In principle, the duration of administration should be 12 months, and safety data should be collected from at least 100 evaluable participants. The number of participants to be enrolled at the start of the study should be determined in consideration of withdrawals, etc.
Dose selection	In principle, the dose should be selected in consideration of the skin concentration that can be expected from the actual method of use at the actual site.
Endpoints	Endpoints (evaluation criteria) and dates and numbers of observation should be selected based on the characteristics of individual study products after consultation with a dermatologist. Any adverse events anticipated from the pharmacological action, nonclinical safety studies, safety information of known ingredients with similar pharmacological action, etc., should be thoroughly considered before setting endpoints.
Observation/ evaluation	During the study, observations and assessments should be performed by a dermatologist. On each observation day, the condition of the application site of the participant should be recorded by photography, and evaluation should also be performed using photos.

In principle, a long-term human administration (safety) study should be conducted with a study design that assumes the overlapped use of the same product and the simultaneous use of lotion, emulsion, cream, pack, etc. containing the same active ingredient. If a new method of use which is not expected at the time of development is to be added, a long-term administration (safety) study shall be conducted again in principle.

For the study product, it is necessary to retain a record of the use status to keep track of the amount used. In doing so, records related to the manufacture of the study product (batch number, date of manufacture, etc.) shall also be retained.

It is necessary to establish a system that can provide appropriate medical care to ensure the safety of participants, such as referral to a dermatologist, in case of adverse events, etc. due to the study product.

If adverse events including photosensitivity reaction are found, the detailed situation, intervention, outcome, etc. related to the findings shall be documented.

(3) Studies related to indications[2]

a. Basic study supporting indications

This study is intended to present the results of basic study on the indications proposed in the approval application from a pharmacological viewpoint, and findings that clarify the mechanism of action, etc. should already be obtained. In addition, at this stage, information necessary to conduct use studies in humans should be sufficiently collected.

In particular, as a basic study to support the indications, it is necessary to confirm that there is no cytotoxicity or unexpected pharmacological effect by examining sufficient exposure (the concentration at the maximum dose that can be applied or the concentration that can be ensured a sufficient safety margin for the concentration at the application site at the actual use) with the assumption of overlapped application and simultaneous application of other products (lotion, emulsion/cream, pack, etc.) containing the same active ingredient. In addition, literature, etc. related to pharmacological actions, etc., of the ingredients or similar ingredients should be sufficiently investigated, and if pharmacological actions, etc. of safety concern have been reported, such actions should also be sufficiently examined.

When a new product combining multiple approved active ingredients that are expected to have similar effects is to be developed, it is necessary to perform a basic experiment of the efficacy and safety of the combination before conducting a use study in humans, and to confirm that the combination does not cause undesirable pharmacological effects, enhancement of effects, enhancement of toxicity, or excess effects deviated from desired mild effects.

b. Study related to use results in humans (Clinical trial)

This study is a use study in humans assuming actual use related to efficacy, etc.

For quasi-drugs with new active ingredients, etc., in principle, a human subject study for examining the actual efficacy, etc. of the product should be conducted under the supervision of a dermatologist, based sufficiently on the results of safety studies and basic studies supporting indications already

[2] For permanent waving agents and hair coloring agents, it is acceptable to apply the "Guidelines for Test Methods to Evaluate the Efficacy of Permanent Waving Agents and Hair Coloring Agents" (Administrative Notice of the Office of Cosmetics, Evaluation and Licensing Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 27, 1997).

conducted.

In the evaluation of efficacy, etc., it is necessary to design the study taking into account whether the effect is as mild as those of other quasi-drugs and to scrutinize whether or not it is appropriate to claim the indications in the approval application. In addition to the efficacy, it is desirable to investigate adverse events and adverse reactions by selecting appropriate safety endpoints with reference to nonclinical data, information obtained from basic investigation, and reports in literature, etc. including those on similar ingredients. For each event, details of the onset and course, seriousness, presence or absence of and details of intervention, and prognosis (course after treatment) should be documented, and the dermatologist involved in the study should determine the causal relationship with the test substance.

In the evaluation of efficacy, it is desirable to use quantitative evaluation methods wherever possible in addition to visual/photographic and palpation evaluation based on the current scientific level. It is also desirable to conduct a placebo-controlled study in a blinded manner. These assessments shall be performed by a dermatologist, a skin doctor with clinical experience equivalent to that of the dermatologist, or a researcher who is under the supervision of the dermatologist and skilled in the assessment. Since quasi-drugs are used by general consumers, their feelings in actual use are also important. Therefore, the efficacy of quasi-drugs should also be examined using questionnaire surveys for participants, etc. The protocol should specify in advance that appropriate statistical analysis methods are to be used for the endpoints and should specify the assessment criteria for efficacy.

4. Handling of overseas study data

It is important that the reliability of the results of human studies conducted outside Japan be ensured, for example, by complying with ICH-GCP.

As a human patch test, a test related to ingredients should be conducted using appropriate control ingredients (ingredients used for similar purposes with sufficient use experience in Japan). In principle, for studies of products used on the face, lips, etc. for a long period of time (lotion, emulsion, cream, etc.), it is also necessary to attach data of application tests performed in Japan or data of use experience.[3]

Regarding a long-term human administration (safety) study and a study related to use results in humans (clinical trial), the results of a study conducted in Japan are required for products with efficacy claims related to melanin or sunlight and products such as permanent waving agents or hair coloring agents, for which the efficacy and safety may differ depending on race or use environment of the product, etc. If a human study is to be conducted outside Japan, the evaluator in the study needs to be a specialist with clinical experience equivalent to or superior to that of a dermatologist in Japan.

[3] "Handling of Data on Studies of Cosmetics, etc. Conducted outside Japan" (PAB Notification No. 231 by the Director-General of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, dated March 12, 1986)