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A Prototype Lip Balm: Summary of Three Dermatological Studies Demonstrating Safety and Acceptability for Sensitive Skin

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Synopsis

Data were generated from three studies to assess the tolerability and acceptability of a prototype cosmetic lip balm. Dermatological assessments of topical compatibility (primary and cumulative irritability and sensitization), photoirritant and topical photosensitizer potential, and acceptability for safe use of a prototype cosmetic lip balm on sensitive skin are summarized. In Study 1, the product was applied to the volunteers' backs under a semiocclusive patch followed by patch removal/reapplication over 6 weeks to assess the irritant and allergic potential of the product. Dermatological assessments were performed at the beginning and end of the study or when there was evidence of positivity or adverse event. Study 2 was conducted by applying the product to the volunteers' backs under a semiocclusive patch, followed by patch removal/reapplication and irradiation of the test area with ultraviolet A (UVA) radiation at various intervals over 5 weeks. Dermatological assessments were performed to assess the product's role in the induction of photoirritancy and photosensitization. Clinical and subjective assessments for acceptability were obtained during Study 3 in volunteers with a diagnosis of sensitive skin and those who used the product as per instructions for use during the study period. The data generated from the three studies demonstrated no evidence of primary or cumulative dermal irritation or of dermal sensitization. In addition, no photoirritation potential or photosensitization potential was observed. As assessed by dermatologic monitoring and subject diary entries, the prototype lip balm did not cause irritation or sensitization reactions when used for 28 days in volunteers with a diagnosis of sensitive skin. Based on these findings, the prototype lip balm can be considered suitable for use for people with sensitive skin.

INTRODUCTION

Lip balms provide an occlusive layer on the lip surface to seal moisture and to protect the lips from external exposures, such as dry air, cold temperatures, and wind. The skin on the lips is thin which increases the vulnerability to dryness (1).

A prototype cosmetic lip balm was developed for use in dry, sensitive skin.

To thoroughly assess the safety and risks, and to ensure the appropriate conditions for product use, cosmetic products require clinical testing in humans. Data generated during

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clinical studies are also important to define the instructions for use, appropriate site of use, and informative product labeling.

Compatibility studies are clinical assessments of the safety of topical products on the human skin. These studies are generally conducted with occlusive or semiocclusive patches (patch tests) or in open models (open tests). These literature-based topical safety protocols consist of repeated applications under maximized conditions, and the absence of adverse reactions indicates that the product is safe for use under the specified test conditions. See Table I.

Compatibility evaluations are performed by a dermatologist and results are interpreted using the ICDRG (International Contact Dermatitis Research Group) scale (2).

Sensitive skin is generally accepted as a subjective cutaneous hyperreactivity to environmental factors, although there is no consensus regarding its etiology, classification, or criteria for diagnosis. Surveys across EU, the US, and Japan estimate that 50% of people believe they have sensitive skin (3,4). Consumer reports of sensitive skin are typically self-diagnosed and appear to be increasing both in women and men. The term sensitive skin has come to be defined as an onset of prickling, burning, or tingling sensation because of ultraviolet light, heat, cold, wind, cosmetics, soap, water, pollution, stress, or endogenous hormones (4). One or several of these factors in combination may lead to greater skin irritation caused by a decreased stimulation threshold of nerve endings (hence a higher response to any stimulus), or by decreased epidermal barrier function, therefore a higher index of skin permeation and an increased irritative response and sensation effect.

From the dermatological point of view, sensitive skin is a skin condition of greater irritability to external stimuli due to several causes. It is a skin hyper-reactive, regardless of the etiology (5). Several conditions may lead to or contribute to the underlying etiology of sensitive skin: dermatoses, such as rosacea, seborrheic dermatitis, atopic dermatitis, and contact dermatitis, and specific sensitizations (allergy) perpetuating the skin sensitivity.

In the development of topical products intended for use in people with sensitive skin, various criteria are critical to consider, including minimizing the number of required

Table I
Types of Compatibility Studies

Study name	Methodology
Primary and cumulative skin irritation	Test product is applied to volunteers in an open-patch, semiocclusive, or occlusive fashion Contact length and timeline for readings are standardized
Photoirritation	Irradiation is applied at the test product application site, typically on the forearm or on the back
Dermal sensitization	Test product is applied to volunteers in a semiocclusive or occlusive patch (on the forearm or on the back) Study consists of three phases: Induction, rest, and challenge
Photosensitization	Test product is applied to volunteers in an occlusive or semiocclusive patch (on the forearm or on the back) Study consists of induction, rest, and challenge phases An ultraviolet light (A-band) is used to irradiate test area

ingredients and using minimal concentrations of ingredients known to be irritants. In addition, the use of ingredients known to be sensitizing or revulsive/hyperaemic/vasodilator agents should be avoided. Thought should be given to the use of ingredients which may play a role in the reconstruction of the epidermal barrier, and the use of fragrances and dyes should be carefully considered (6).

Functionally, for the study of a product intended for sensitive skin, volunteers with a clinical diagnosis of sensitive skin are recruited. A method used for assessing the level of skin sensitivity is the "stinging test," which is a straightforward, reliable way to identify the required study population (7).

Data generated from three studies with the prototype lip balm are summarized herein. Study 1 was designed to demonstrate the absence of irritant (primary and cumulative dermal irritation) and allergic (sensitization) potential of the product. Study 2 was designed to demonstrate the absence of photoirritation or photosensitization of the product when exposed to UVA radiation through the phototest assay. The objective of Study 3 was to prove the suitability, under normal conditions of use, of the product for people with a diagnosis of sensitive skin.

MATERIALS AND METHODS

The three studies described herein were sponsored by GlaxoSmithKline Brazil Ltda. and conducted at the Medcin Instituto da Pele Ltda. clinical research site in São Paulo, Brazil. The Medcin Instituto da Pele has a Quality Management System that is in compliance with Good Clinical Practices (GCP) guidelines and Number Standard International Organization for Standardization/International Electrotechnical Commission 17025/2005, which specifies the general requirements for assessing the qualification of assay and calibration laboratories. The quality control is performed in every step of the method described in the protocols to allow the investigation and the accurate assessment of the test product, ensuring the reliability of data analyzed according to standard procedures. The studies were conducted in accordance with GCP regulations, the Declaration of Helsinki, and the Rules on Research Involving Human Subjects (Resolution National Health Council 196/96 and others) per the National Health Council, Brazilian Ministry of Health.

The list of ingredients in the study product includes purified water, butyrospermum parkii butter, D-glucose-monohydrate, olus oil, elaeis guineensis oil, glycerin, oryza sativa cera, behenyl alcohol, oryza sativa bran oil, hydrogenated lecithin (hydrogenated phosphatidylcholine), capryloyl glycine, pentylene glycol, caprylyl glycol, hydroxyethyl cellulose, squalane, sodium hydroxide, dehydroxanthan gum, dl-alpha tocopherol, galactoarabinan, acrylates/C10-30 alkyl acrylate crosspolymer, sodium carbomer, palmitamide monoethanolamine, trisodium ethylenediamine disuccinate, ascorbyl palmitate, ceramide 3, and phytosphingosine.

In the observational studies 1 and 2, the product and controls were applied to the volunteers' backs under patches and dermatological assessments were performed at specified times per protocols or when there was evidence of positivity (grade 2, 3 or 4 on the ICDRG scale) or an adverse event.

The patches were semiocclusive and were comprised of 1 cm in diameter filter paper discs (100% cellulose) and Micropore® semipermeable adhesive tape.

The study product (undiluted), 0.02 mL, was applied under a patch to the volunteers backs along with the following controls under a separate patch each:

- Saline solution
- Mineral oil
- No product on the filter paper disc
- Adhesive tape (Micropore® with no filter paper disc).

During the studies, volunteers were instructed not to move or wet the patches, not to start using new topical products during the assessment period, and not to be exposed to direct sunlight. Volunteers were requested to report the use of any medication or treatment during the studies.

Dermatological assessments for studies 1 and 2 measuring dermal irritability and sensitization, photoirritation, and photosensitization, were performed using the scale recommended by the ICDRG (2). See Table II.

If any evidence of positivity was observed (grade 2, 3, or 4), a new reading was performed after 30 min at rest, and if the evidence remained unchanged, the volunteer was referred to a dermatologist. In the case of positivity evidence confirmed by the dermatologist, the application of the sample would be discontinued and a retest would be performed on the volunteer. For these situations, the adverse event was followed up as required until event resolution.

If a retest was required, a semiocclusive patch containing the sample suspected of positivity was applied on an application-naive area of the volunteer's back or forearm. Sample reapplication would be performed on the same day on which the reaction was observed if the reaction was classified as mild in accordance with the ICDRG reading scale. If the reaction was classified as moderate or severe, the sample reapplication was performed in a minimum of 48 h. Readings were performed 24 h after application to determine positivity.

Studies 1 and 2 were conducted in healthy volunteers of both genders between 18 and 60 year of age who were classified with skin type as Phototype I–IV per the Fitzpatrick scale, a numerical classification scale, which classifies a person's complexion and their tolerance to sunlight and ultraviolet radiation (8).

Study 1 consisted of three phases of separate assessments for primary dermal irritation, cumulative dermal irritation, and dermal sensitization.

In the primary dermal irritation phase, patches were removed after 2 d (48 h) and the initial assessment was conducted. A second assessment was made 2 d later (96 h) after a patch free interval. Assessments at 48 and 96 h were recorded.

In parallel to the primary dermal irritation phase, patches were applied to a separate area of volunteers' backs to assess cumulative dermal irritation. Volunteers returned for patch

Table II
ICDRG Scale

ICDRG reading	Result	Grade
No lesion	Negative	0
Mild erythema	Uncertain	1
Clear erythema	Positive (+)	2
Erythema + edema + papules	Positive (++)	3
Erythema + edema + papules + vesicles	Positive (+++)	4

assessment and reapplication for 3 weeks at 48 h intervals or 72 h intervals over a weekend (±1 d) for a total of eight applications.

After the last assessment for cumulative dermal irritation, the sensitization (challenge) phase of the study was initiated. Volunteers completed a 2-week wash out period, and then returned to the clinic for the application of patches with test product and controls to skin areas on the back or forearm that had not been previously occluded. After 48 h, the patches were removed and initial sensitization assessments were recorded. Volunteers returned the following day for their 72-h assessment.

Study 2 consisted of two phases of separate assessments for dermal photoirritation and dermal photosensitization.

For the assessment of dermal photo irritation, patches with test product and controls were applied to volunteers' backs; after 2 h, the patches were removed and the patch area was irradiated by UVA-emitting equipment at the 10 J/cm2 dose. The volunteers returned after 24 h for a dermal assessment of the patch area.

In parallel to the photo irritation phase of the study, the accumulated photosensitization effect was measured. On day 1, patches with test product and controls were applied to a different area of volunteers' back. During a 12-d period, the procedure included the removal of the patches, the UVA irradiation to the area at 4 J/cm^2 dose, and the reapplication of the patches on days 2, 4, 5, 8, and 10.

On day 12, the patches were removed and irradiation performed. After the last irradiation, volunteers were off product for 2 weeks and then returned for a challenge phase. Two sets of patches containing the same test product and controls were applied to volunteers' back in areas that had not been previously occluded. Twenty-four hours later, volunteers returned for patch removal. One area received UVA irradiation at 4 J/cm^2 dose, and the other area received no irradiation. Assessments were performed on both areas 48 h after irradiation.

After the last assessment, volunteers had a new dermatological assessment performed to compare the baseline and end of study skin condition.

Study 3 was a single-center, noncomparative, blind study, where the product was assessed at the site of use (on the lips) for 28 ± 2 d in volunteers with a clinical diagnosis of sensitive skin. Assessments performed by dermatologists were conducted at the beginning and end of the study.

The study was conducted in healthy volunteers of both genders between 18 and 60 years of age who met criteria of sensitive facial skin as diagnosed using the stinging test procedure (7), as follows:

Two different cotton swabs were soaked, one with 10% lactic acid and the other with saline solution, and applied in different areas of the volunteer's alar groove. Five minutes after the application, the grade for sensation of burning was recorded, according to the following scale: 0 - None, 1 – Little, 2 – Moderate, and 3 – High/Severe. Volunteers reporting a grade of ≥2 meet the criteria for Sensitive Facial Skin.

After confirmation of sensitive skin diagnosis, the tubes of test product, including instructions for use (as many times as needed, at least twice daily) and the Diary of Use, were dispensed to the volunteers. Volunteers were provided instructions for the correct completion of the diary (date, number of times the test product was applied and whether there were any sensations of discomfort) and were required to bring the completed diary

to their last study visit. The volunteer was instructed to go to the Institute for a medical assessment in case he/she experiences any discomfort during the study period.

After 28 d of use, the volunteers returned to the Institute for a new dermatological assessment to assess skin integrity and whether or not there had been the formation of erythema, edema, desquamation, vesiculation, or other clinical signs and/or symptoms at the site where the product had been applied. A tolerance of ±2 d was allowed for volunteers to return for their final assessment.

At the study end, the volunteer answered the Subjective Assessment (redness, itching, swelling, desquamation, small spots, small blisters, marks, and burning) to identify potential signs and/or symptoms seen during the study, according to his/her self-perception.

RESULTS

The studies provided robust data to assess the irritation and sensitization properties of the prototype lip balm.

The demographics of the studies are described in Table III. Most subjects were female, with a broad distribution of enrollment for age range of 18–61 years targeted for inclusion in studies.

Of the 99 subjects who enrolled in the three studies, 92 completed study obligations and provided data for the analyses.

There were four subjects lost to follow-up, one subject in Study 1 (did not attend visit three onward and withdrew consent for personal reasons) and three subjects in Study 3 (did not attend the final study visit or respond to efforts to contact them). Thus, these volunteers were discontinued from the studies and their data were not considered (Table IV).

There were two subjects who discontinued due to protocol violations (Table IV), both subjects were withdrawn from the respective study for using an anti-inflammatory drug during the study period. One subject in Study 1 was withdrawn from the study when she presented with erythematous papular lesions in the posterior chest area (eczema) on day 3 (Table IV). According to the medical evaluation, the lesion was classified as moderate and the diagnostic hypothesis as contact eczema probably related to the glue from the adhesive tape (Micropore®). The subject discontinued the use of the test product patch without any new challenge. Treatment with Diprogenta (betamethasone dipropionate 0.64 mg + betamethasone 0.5 mg + gentamicin 1 mg) was administered twice daily for 5 d; the subject was subsequently evaluated in 7 d and the Diprogenta treatment was discontinued as the adverse event had resolved with no sequelae.

Table III
Demographic Data for Subjects that Completed Studies 1–3

	Study 1	Study 2	Study 3
Subjects completed	52	30	30
Male	5	3	4
Female	47	27	26
Age range (year)	18–60	21–60	23–60
Median age (year)	39	37	47.5

Table IV
Number of Adverse Events and Discontinuation Data for Subjects in Studies 1–3

	Study 1	Study 2	Study 3
Subjects enrolled	55	31	33
Subjects completed	52	30	30
Number of adverse events	2	0	0
Reasons for discontinuation			
Lost to follow-up	1	0	3
Protocol violation	1	1	0
Adverse event	1	0	0

In addition to the subject who withdrew from Study 1 due to the presentation of moderate eczema, there was one additional clinical sign of skin discomfort reported in Study 1 as shown in Table V. The mild skin irritation reported in this subject was thought to be influenced by the weather conditions during the study period and did not impact the data generated during the study observation period. Patches were reapplied at the next visit and the subject did not experience any further discomfort or irritation. There were no reports by any subjects of skin discomfort during the conduct of Studies 2 and 3.

Under the conditions of assessment, Study 1 showed that the prototype lip balm had no primary dermal irritation potential, cumulative dermal irritation potential, or dermal sensitization potential.

No photoirritation potential or photosensitization potential was observed in any of the 30 volunteers who completed Study 2.

Of the 30 volunteers who completed Study 3, none experienced any adverse skin reaction under close dermatological monitoring. In addition, the analyses of Diary of Use entries provided at the end of the study period by the subjects indicated no reports of discomfort on the lips during the 28 d of product use. The product did not cause irritation or sensitization reactions and can be considered suitable for use in people with sensitive skin.

DISCUSSION

In the two cases of contact eczema observed in Study 1, the first case was medically evaluated and classified as moderate with the diagnostic hypothesis as contact eczema probably

Table V
Clinical Signs of Skin Discomfort in Study 1

Subject	Event	Severity	Relation to test product	Subject discontinued from study
08	Contact Eczema	Moderate	Unlikely related (investigator deemed event likely due to glue from the adhesive tape/Micropore patch)	Yes
42	Contact Eczema	Mild	Not related (investigator deemed event likely due to glue from the adhesive tape/Micropore patch)	No

related to the glue from the adhesive tape (Micropore®). This hypothesis was based on the location of the irritation being observed under all patched sites under the adhesive tape in the posterior chest area.

The second case was a report of mild skin irritation which was thought to be influenced by the weather conditions during the study period, as the study was conducted during the summer months. This did not impact the data generated during the study observation period.

The data from the three studies described herein, summarizing the dermatological assessments of topical compatibility (primary and cumulative irritability and sensitization), photoirritant and topical photosensitizer potential, and acceptability under normal use conditions, support the use of the prototype cosmetic lip balm as a suitable product for use on sensitive skin.

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