[redacted]

[redacted]

[redacted]STANDARD PROTOCOL #100

REPEATED INSULT PATCH TEST (RIPT)

[redacted]

1.0 TITLE OF TEST: REPEATED INSULT PATCH TEST (RIPT)

2.0 PURPOSE: The purpose of this test is to evaluate the potential of the Test Material (TM)*, as a result of repeated applications, to induce dermal sensitization in humans. This Protocol is appropriate for cosmetic and other non-prescription topically applied TM, including OTC products, ingredients, fibers, papers, wipes, fabrics and / or other materials, for which the dermal application to humans is not regulated by the USA government. Unanticipated and unforeseeable changes in the TM / tests may necessitate the alteration of any provision of the Protocol. The changes shall be documented in the Test Folder and the Final Report; as appropriate, the IRB shall be notified. All other provisions of this Protocol shall continue to apply. This Protocol is structured upon the guidelines outlined in Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, April, 1996.

3.0 INVESTIGATORS:

[redacted]

Lynne B Harrison, PhD, Principal Investigator (PI)**

[redacted]

4.0 IRB APPROVAL: This Protocol and the Informed Consent Form have been approved by [redacted]

5.0 TEST MATERIAL: A Letter of Authorization (see Appendix I) shall be sent from the Sponsor. This letter serves as an Appendix to this Protocol and shall contain a description of the TM, specific preparation and testing instructions and a statement as to the safety for testing on humans. Safety information shall be sent from the Sponsor—the HRL Safety Assurance Form (see Appendix II), or equivalent, must be completed and signed by an authorized, qualified representative of the Sponsor. It is the responsibility of the Sponsor to notify HRL in writing, about all regulated ingredients and to list the concentration of each regulated ingredient and also to inform HRL about all ingredients that must be disclosed to the IRB and to the human subjects. In addition, the Sponsor must document the allowable concentration for each regulated ingredient, as it is used in the specific TM on Appendix II. In time-dependent situations, verbal instructions shall be accepted by HRL; these instructions shall be followed up by the Sponsor in writing.

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* Throughout this Protocol, "Test Material" or "TM" shall be understood to be singular or plural, as appropriate.

** Throughout this Protocol the designation of a technical staff member shall be understood to include her / his designated assistants.

5.0 TEST MATERIAL: (continued) Each TM is received from the Sponsor, who shall provide the following per 100 subjects:

A) Liquids, including lotions: approximately 1.0 liter (approximately 32 oz),

B) Solids: approximately 1.0 kg (approximately 2 pounds),

C) Fabrics, fibers, sheetings, etc.: at least 1,500 pieces if pre-cut by the Sponsor, or 3000 cm^2 (approximately 1200 in^2) if not pre-cut.

The Sponsor shall provide instructions as to any required dilution (including diluent), preparation method if applicable, and special storage instructions (including refrigerating, freezing, or heating) of the TM.

If requested by the Sponsor, a record of the TM weight, upon receipt and at the end of the test, shall be kept. The recording of weights, for products in containers pre-filled by the Sponsor, shall be the responsibility of the Sponsor and accepted by HRL as stated.

If at any time during the test the Sponsor changes the instructions pertaining to a TM or testing procedures, verbal instructions shall be accepted by HRL; these instructions shall be followed up by the Sponsor in writing.

If the Sponsor supplies a TM in multiple containers, the Sponsor warrants that the TM is from the same batch / lot, or as noted by the Sponsor.

6.0 SUBJECTS: Panels shall consist of the number of human subjects required by the Sponsor. Sufficient contingency subjects shall be empanelled to attempt to insure completion of the required number.

Each first-time subject shall complete an HRL Subject History Form: (HRL Form:SHF), including relevant medical history, and a Permission To Release Personal Health Information Form in conformity with the Health Insurance Portability and Accountability Act (HIPAA). (An updated SHF shall be secured approximately every 18 months.) Each subject shall also complete a W-9 form and provide proof of age. Each accepted subject shall be assigned (or shall have been assigned) the next sequential permanent HRL Identification Number from the HRL master list of assignable numbers.

Legally valid written informed consent, in conformity with: 21 CFR 50.25, Subtitle A, Protection of Human Subjects, Approved by an IRB, shall be secured from each subject. Subjects will be given a copy of the Informed Consent To Participate In a Research Study Form together with printed Panelist Instructions and relevant ingredient information.

6.1 Inclusion Criteria:

- Sex: Male or female.
- Age: Over 18 years. (The age of each subject on Test Day 1 will be recorded. This age shall be considered the subject's age throughout the test.)
- Good health as determined from the HRL SHF.
- Signed and dated Informed Consent Form.
- Signed and dated HIPAA Form.

[redacted]

6.0 SUBJECTS: (continued)

6.2 Exclusion Criteria:

- Subjects on test at any other research laboratory or clinic.
- Known allergy or sensitivity to cosmetics and / or toiletries, including sunscreens, adhesives and / or topical drugs and / or ingredients included in the specific test.
- Pre-existing dermatologic conditions which have been diagnosed by a medical professional (e.g., psoriasis, eczema, etc.) which would interfere with this study.
- Pre-existing other medical conditions (e.g., adult asthma, diabetes).
- Treatment with antibiotics, antihistamines or corticosteroids within two weeks prior to initiation of the test.
- Chronic medication which could affect the results of the study (e.g., insulin, corticosteroids, antihistamines, steroidal or non-steroidal anti-inflammatory drugs [except for therapeutic maintenance dosage of aspirin], antibiotics, steroid inhalers, etc.). See Attachments I and II, letters from Deborah R Spey, MD, FAAD, a Board-Certified Dermatologist and an HRL Consulting Dermatological Co-Investigator.
- Known pregnant or nursing women.
- Cancer diagnosis within the previous 5 years.

On exclusive Panels, if requested by the Sponsor, the Panel may consist of "sensitive" subjects or have any other specific demographic and / or biological parameters.

An appropriate clearance time from the end of one test to the beginning of the next test shall have elapsed as per HRL SOP: RECRUITMENT / ENROLLMENT / CONSENTING.

7.0 METHOD: The RIPT shall be performed as per HRL SOP:RIPT. The Project Manager shall note all special Protocol requirements and TM preparation / storage requirements and shall post them in the designated area of the Patch Room.

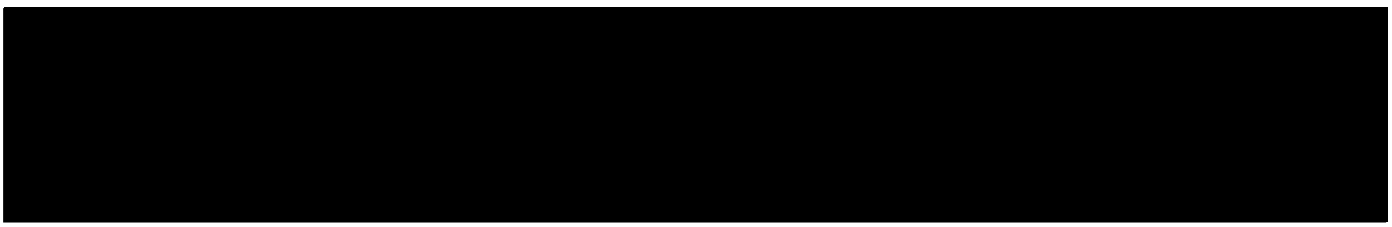
Each TM shall be applied for a total of 9 Induction applications, followed by an approximately 2 week rest period. The rest period will then be followed by an approximately 24 - 48 hour Challenge application.

7.1 Patch Preparation: A webril/adhesive patch (Covidien Patch #4022 or equivalent) shall be used occlusively; the patch may be altered to be semi-occlusive, if requested by the Sponsor. The Sponsor may specify any other patch. The TM may be applied directly to the skin; this may then be covered with a semi-occlusive patch, or allowed to dry as an "open" patch, or may be removed after a period of time.

For liquid materials, approximately 0.2 gm, or other amount specifically required by the Sponsor, shall be applied to each test site / patch.

For solid materials, approximately 0.2 gm, or other amount specifically required by the Sponsor, shall be applied to each test site / patch.

For fabric, fiber, sheeting or similar materials, approximately 1-2 cm^2, or other amount specifically required by the Sponsor, shall be applied to each test site / patch. Any



7.0 METHOD: (continued)

7.1 Patch Preparation: (continued) required wetting shall be with physiological saline, distilled water, tap water, etc., as per the Sponsor's instructions. Tapes and / or bandages may be applied directly to the skin.

For TM with particular characteristics / specific gravity / spreadability / thickness, HRL shall confer with the Sponsor in regard to the amount placed on the test site / patch.

7.2 Test Sites: Eligible test sites shall be as per HRL SOP:RIPT. The test sites shall be recorded on the anatomical diagram of each subject's individual Data Form.

The patches shall usually be applied to the back. The position of the patches shall be marked with gentian violet surgical skin marker, or equivalent. The subjects shall be instructed to keep the patches dry and untouched. The subjects may be instructed to remove the patches themselves. On exclusive panels, the Sponsor may request that the patches be removed at HRL. Patches may be reinforced with tape.

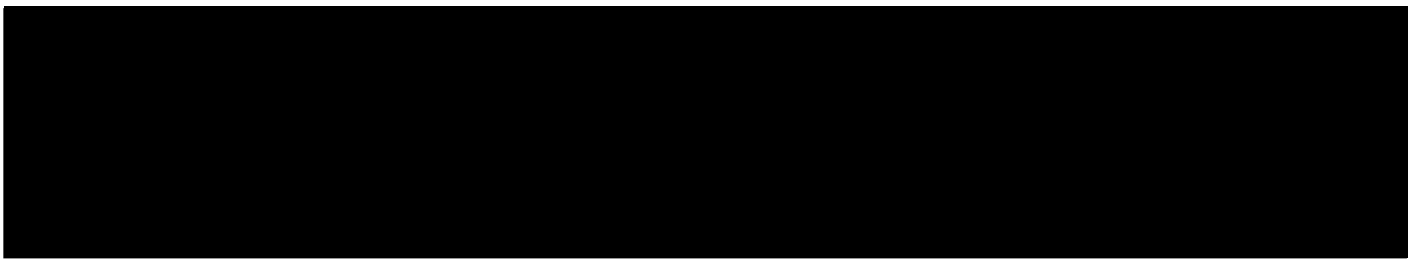
Subjects shall be cautioned to protect the test sites from exposure to sunlight or sunlamps throughout the test period and not to use heating pads or heated car seats on the test area. Subjects will be instructed not to apply any product (including sunscreens) to the test area after patch removal and to try not to wash off the marks.

7.3 Test Schedule: Permitted scheduling shall be as per HRL SOP: RIPT. Each test site shall be scored as per the Scoring System; see 7.4 below.

A. Induction Phase: Each TM shall be applied to the designated test site for a total of 9 Induction applications in a period of approximately 3 weeks. The patches shall remain in place and the area kept dry for approximately 24 – 48 hours, at which time the subject or HRL technician shall remove the patches. On exclusive panels, subjects may be requested to come to HRL for patch removal. Either immediately or approximately 24 – 72 hours after removal of the patches, the test sites shall be scored by the Project Manager and the scores recorded on the Data Form prior to re-patching. Fresh TM and patches shall be applied to the identical test sites until 9 Induction patchings are completed.

If a subject develops a 2-level or greater reaction or an edematous reaction (or equivalent in any Sponsor-specific scoring system), the test site may be changed to a new site. A test site may be changed at the request of the subject. If a 2-level, or greater, or edematous reaction (or equivalent in any Sponsor-specific scoring system) is observed at the changed test site, the subject shall not be re-patched with the TM during the balance of the Induction Phase, but may be Challenged at the regularly scheduled time. The decision whether to Challenge a subject who is judged to be pre-sensitized will be made on a case-by-case basis.

A subject may miss one or more regularly scheduled Induction patchings and may make up the missed patchings during the Induction Phase. A subject may make up missed patchings at the end of the Induction Phase or the subject may be discontinued.



7.0 METHOD: (continued)

7.3 Test Schedule (continued)

B. Rest Phase: A rest period of approximately 2 weeks shall follow the application of the last Induction patches; no TM shall be applied during this rest period. The preferred minimum rest interval is 10 days and the preferred maximum is 21 days. Subjects are instructed to notify HRL and if possible to return to HRL if any reaction develops during the Rest Phase.

C. Challenge Phase: Following the rest period, a Challenge patch of each TM shall be applied to a virgin site. Approximately 24 - 48 hours later, the patches shall usually be removed at the laboratory, the Challenge test sites scored and the scores recorded on the Data Form. The test sites shall be scored and the scores shall be recorded on the Data Form again at approximately 48 hours, approximately 72 hours and approximately 96 hours post-patching.

If a subject misses a Challenge Phase scoring visit, the subject will either be discontinued or the visit may be made up. Each Challenge Phase missed visit will be handled on a case-by-case basis. Appropriate notations will be made in the Notes section of the subject's Data Form.

If a score of 2, or greater, or an edematous reaction (or equivalent in any Sponsor-specific scoring system) is observed, appropriate Re-Challenge / Re-Test procedures shall be discussed with the Sponsor. Subjects shall be instructed to notify HRL if any reaction develops after the test has ended.

[redacted]

8.0 ADVERSE REACTIONS / EVENTS: Each subject will be instructed to communicate with HRL immediately if she / he has any reactions / problems with any TM. Any and all Adverse Reactions will be reviewed by the Investigator as soon as possible after HRL has been notified of the occurrence. The Investigator will attempt to assess the relationship of the reaction to the TM and report her findings. Further, the Sponsor will be notified of any reaction and a proper course of treatment will be discussed. Erythema, edema, dryness, stinging, peeling, itching, burning, tape reaction and hyperpigmentation / hypopigmentation are possible, expected endpoints and are not to be considered Adverse Reactions necessitating a report to the IRB.

In addition, any and all Adverse Events will be reviewed by the Investigator as soon as possible after HRL has been notified of the occurrence and an Adverse Event Form will be completed. IRB and Sponsor notification shall be as appropriate. Sponsors may supplement and / or replace HRL's procedures and / or forms prior to authorizing any test.

9.0 INDEMNIFICATION: The Sponsor shall indemnify and hold HRL harmless against all liability, claims, demands, damages, reasonable costs and expenses, including but not limited to attorneys' fees, whether for injury to person or persons or damage to property, arising out of, resulting from or occurring, or alleged to have risen out of, resulted from or occurred, during the course of the testing done for the Sponsor. HRL shall notify the Sponsor of any such claims. Indemnification by the Sponsor shall not apply in any situation where the claim or demand or alleged liability or damages was caused by the negligence of HRL or its employees.

10.0 QUALITY ASSURANCE: To assure compliance with the Protocol and HRL SOPs, the internal Quality Assurance Unit shall perform an in-phase audit during the conduct of the study, and complete an audit of the study records and Draft and Final Reports as outlined in HRL SOPs, using a random sampling approach.

11.0 REPORTING: A Final Report shall be issued for each TM. The Final Report shall include a statement of the Purpose of the test, description of the TM, criteria for Subject Selection, explanation of the Method, Results and Conclusions. Tabular presentation shall be made of the subjects' demographic data and dermal responses. At the Sponsor's request, reporting may be modified to omit or add any sections.

12.0 RETENTION: All original Data Forms shall be retained for at least 3 years. A laboratory retainer bottle of each TM shall be retained for at least 2 years.

Return or disposal of unused TM shall be as per the Sponsor's instructions. HRL shall appropriately dispose of any TM after 6 months if no Sponsor instructions have been communicated.

13.0 RECORDS TO BE MAINTAINED:

13.1 Protocol: HRL shall have on file a copy of this Protocol, signed and dated by both the HRL Principal Investigator and the Sponsor's Representative.

13.0 RECORDS TO BE MAINTAINED: (continued)

13.2 Letter of Authorization: A sample letter of Authorization is appended as Appendix I, containing the elements required by HRL.

[redacted]

[redacted]

[redacted]

Date: _____ Company: _____

Test Material/Formula #: _____

Name of Test Material under which Final Report should be written, if applicable: _____

_____

Number of subjects required: _____ P.O. # (if applicable) _____

Test Material Preparation: Check all that apply.

Test as Received ☐
or
Prepare as follows: Dilute to _____% ☐ v/v ☐ w/w ☐ w/v ☐ v/w

in: ☐ tap water ☐ distilled water ☐ mineral oil

☐ other: explain _____

Patch Type: ☐ occlusive ☐ semi-occlusive ☐ "open patch"

☐ other: explain _____

Patching Method: ☐ volatilize for _____min ☐ discard patches after _____min

☐ patch _____ side to skin ☐ moisten patches with _____

☐ other: explain _____

Test Material Storage Conditions: ☐ Room temperature (50° - 85°F) ☐ Refrigerate ☐ Freeze ☐ Other

Additional Instructions/Modifications to Standard Protocol: _____

_____

Safety Information: _____

_____

SPONSOR CERTIFICATION:
It is the responsibility of the Sponsor to Certify the appropriateness and the safety of the Test Material for testing on human subjects as described above at the agreed upon concentration. The Sponsor further Certifies that this Test Material is a cosmetic and/or ingredient for which the dermal application to humans is not regulated by the USA Government.
By our submission to HRL of Appendix I and II for testing of the above-mentioned test material, we agree to the terms and procedures described in HRL Protocol #100.

_____

Sponsor's Signature Date

_____

Print Name Title

[redacted]

SAFETY ASSURANCE FORM

Prior to performing any tests on human beings, HARRISON RESEARCH LABORATORIES, INC. requires the following assurance of safety:

All of the ingredients in the Test Material are Food and Drug Administration (FDA) Category I ingredients—Generally Regarded As Safe and Effective, and/or are included on GRASE lists and are not prohibited ingredients and/or have been reviewed by CIR and/or have a history of safe use and I can certify that the dermal application to humans presents no unusual risk to the test subjects. Where applicable, and unless otherwise noted, all of the ingredients are used at approved concentrations.

Please list all ingredients and concentrations for which the dermal application to humans is subject to any United States of America government regulations.

COMPANY NAME_____

AUTHORIZED REPRESENTATIVE_____

ADDRESS_____

_____

TELEPHONE #_____E-Mail address:_____

FORMULA #_____

Type of Test Material / Intended Use:_____

REGULATED INGREDIENTS None ☐ or

Please list any ingredients that are regulated / active, etc. as used in this formulation, that must be disclosed to the IRB and the human subjects.

List regulated ingredients: Name	Concentration	Allowed Concentration

_____

Sponsor's Signature Date

_____

Print Name Title

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