Clinical Safety Testing 101 Understanding Safety Testing For The Cosmetics and Personal Care Industry

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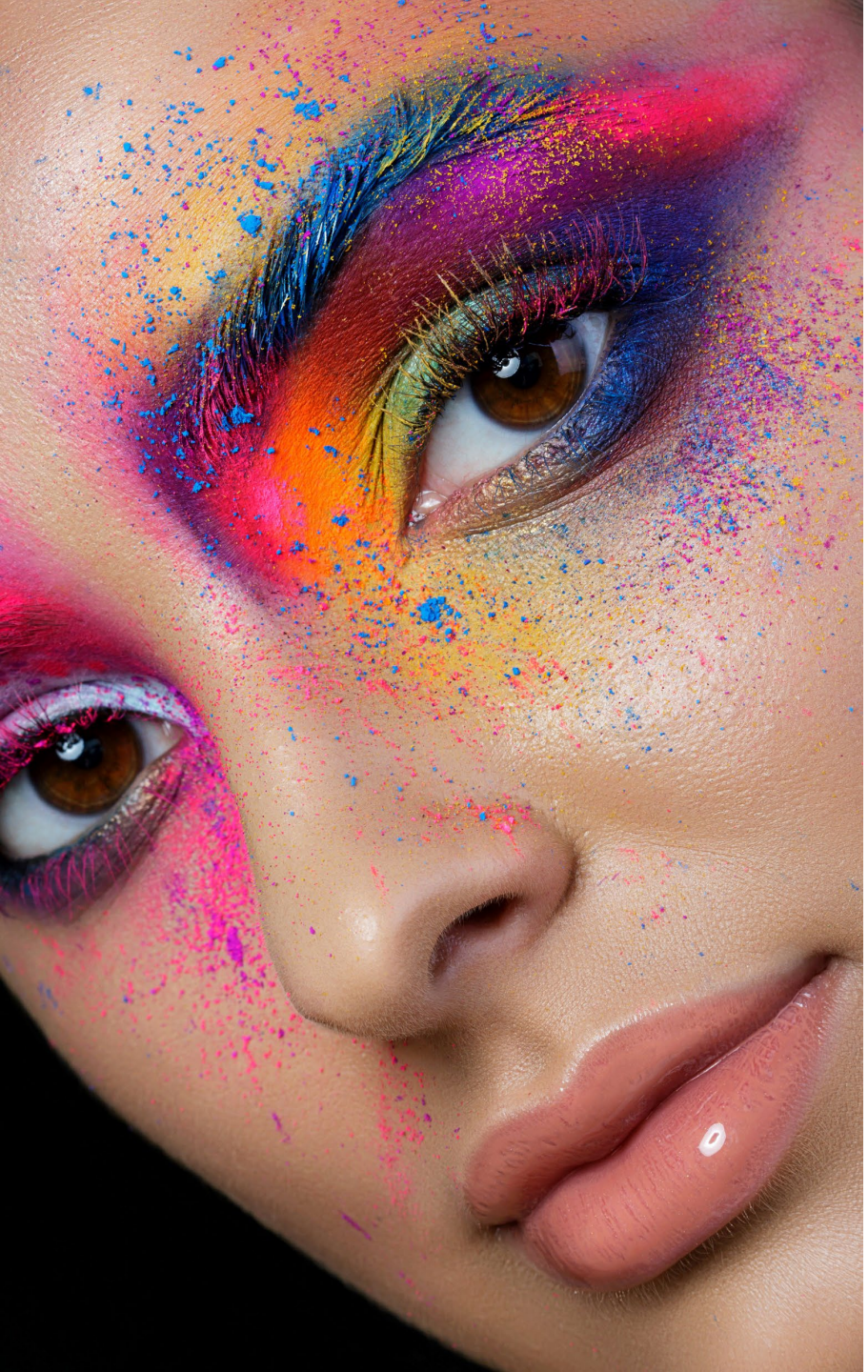
Who is Responsible for Substantiating the Safety of Cosmetics?

- Companies and manufactures have the legal responsibility to ensure the safety of their products.
- Other than color additives, cosmetic products and ingredients do not need FDA approval before going to market in the U.S.
- Companies and manufactures need to follow the following two laws pertaining to cosmetics, they are the most important and are FDA regulated.
  - Federal Food, Drug, and Cosmetic Act (FD&C Act)
  - Fair packaging and labeling Act (FPLA)



Are You Wondering What Products Are Considered Cosmetics to the FDA? Per FDA Cosmetics are:

Articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance" (FD&C Act, sec. 201(i)). Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product. It does not include soap.

My Product is Not a Drug or Soap, It is a Cosmetic… Now What?

3 Areas of Testing that Should be in Any Cosmetic Product Profile on the Market:

1. Stability Testing: Used to determine if a cosmetic can be altered or become unsafe depending on environmental conditions.
2. Micro Testing: Does your preservative system hold up to consumer use? This testing ensures that there is no harmful microorganism growth.
3. **Safety Testing: Patch Testing or Safety In Use Testing = Clinical Safety Testing on Human Subjects- This will be our focus today!**

My Cosmetic Product has Successfully Completed Stability and Micro Testing… Now What?

Patch Testing

- **HRIPT's-** Main goal is to determine a potential for inducing sensitization. Can also determine the potential for eliciting dermal irritation.
- **Primary Irritation Test-** Assesses the product's likelihood of causing irritation after one patch application.
- **Cumulative Irritation-** Assesses the product's likelihood of causing irritation after multiple patch applications. Has the possibility of detecting weak irritants.

Safety-in-Use Studies

- Determines the potential of a product to elicit an irritant response under real-life use conditions.

HRIPT Overview

Human Repeated Insult Patch Test (HRIPT)

- Recommended sample size: 200 subjects
- Can be used for most cosmetic and personal care products
- Varying patch types (Occlusive or Semi Occlusive, Finn Chambers)
- Varying product dilutions – for products that are diluted when used in real use setting such as shampoo, body wash, face wash
- Objective of RIPT Study – 2 Fold

Test for both Skin Irritation and Skin Sensitization

RIPT Study Design

24 - Hour RIPT

- 6-week study that includes a rest period of 10-21 days totally 15 visits.

Induction Phase (Irritation Phase)

- Patches containing test materials are applied to the same location on the UPPER back three times per week (M,W,F) for a total of nine applications. Patches remain in place for 24-hours. Sites are graded for irritation at each visit.

Challenge Phase (Sensitization Phase)

- Subjects return from their break (10-21 days), patches containing test materials will be applied to a virgin site LOWER back. Subjects return to the lab 24-hours after application for patch removal and grading. Subjects must also return for evaluations at 48, 72, and 96-hour evaluations.

RIPT Studies

Patch Types

- **Semi-Occlusive**- Breathable tape/adhesive surrounds the gauze center. Most products should be tested using semi-occlusive patches.

- **Occlusive-** Non-Breathable tape/adhesive surrounds the gauze center- Products that are used under occlusion such as hand prep treatments used under latex gloves or scalp treatments, products used under bandages (all sound like drugs, right?) – Most cosmetic products do not warrant RIPT testing under Occlusive conditions. It is overkill.

RIPT Studies

Dilutions and Volatizations

What products should be diluted for RIPT testing?

- Any product that needs water when used by the consumer
- Shampoo, Conditioner, body and face wash, hand wash, etc.

What products should be volatized for RIPT testing?

- Any product that has a high alcohol level should be volatized at least 15 minutes before patching

RIPT Studies

What is concluded at the end of the study

RIPT conclusions can come in a few different forms:

1) Product showed potential for Irritation but not Sensitization: Reactions were observed in 10% or more of the study population in the induction phase.
2) Product showed no potential for Irritation but showed potential for Sensitization: One or more strong reactions were observed in the challenge phase of the study. Sensitization is an allergic response to a product. In this case a re-challenge will be performed to confirm sensitization.
3) Product showed potential for Irritation **AND** Sensitization: Reactions were observed in both the Induction and Challenge phase of the study.
4) Product showed no potential for Irritation **OR** Sensitization: No reactions were observed at all.

RIPT Studies

Re-Challenge

If the reactions observed in the challenge phase are indicative of sensitization (edema is usually observed) a re-challenge is recommended.

- One week repeat of the challenge phase that will take place no sooner than 10 days from the last challenge phase.
- The test material is applied to a virgin site under the same conditions of the challenge phase and the subject is examined for dermal irritation.
- At the Sponsor's request, additional ("omission product" or individual components) may be tested, and/ or other test conditions may be used.

RIPT Studies

Other considerations for RIPT Testing

Number of Subjects tested:

- n=50, 100, 200: Finished products should be tested on no fewer than 100 subjects.

Why? :

1% of the general population will have a reaction to cosmetics and personal care products. If 1 out of 50 subjects reacts to your product, you are already over the 1% acceptability threshold of reactivity to products on the market. Testing on a larger population allows for a larger sampling of the real-world users of your product.

Why offer n=50 testing then?

50 subject RIPT panels are useful for situations such as:

- Minor formulation changes, retesting to confirm past RIPT results

Why offer n=200? : A successful 200 subject RIPT is the industry accepted standard for claiming "Hypoallergenic" on your product label.

RIPT Studies Broken Down

Other considerations for RIPT Testing- Part II

What if I have an eyeshadow set with 10 shades, Do I need to test all 10 shades on RIPT?

- Most Conservative Answer: Yes, each individual shade should be tested to ensure that you have a complete safety profile on each shade
- Less Conservative Answer: No, You can choose to make a set of composite shades for testing.
- For Example: composite (combine) 3 shades and submit the “mix” as one sample for RIPT testing. Note: Not recommended to test more than 3 shades in a composite. Second Note: Be prepared to do further RIPT testing if you see a reaction on a composite.

Primary Irritation Studies

Duration:

24-hour: Patches containing test materials remain in place for 24-hours. Subjects will have the test site evaluated at 24-hours and 48-hours.

48-hour: Patches containing test materials remain in place for 48-hours. Subjects will have their test sites evaluated at 48-hours and 72-hours.

Sample Size:

50 subjects

Conclusion:

Primary irritation potential will be determined by using the primary dermal irritation index (PDII). This method calculates the erythema scores.

Erythema Score	Frequency of Erythema Scores	Frequency Total (= Erythema Score x Frequency of Erythema Scores)
0	10	0.0
0.5	6	3.0
1	2	2.0
2	2	4.0
3	0	0.0
4	0	0.0
	Total	9.0
	PII (total score/sample size)	9.0/20 =0.45

Cumulative Irritation Studies

Duration:

14-Day: Patches containing test materials are removed and reapplied everyday for the duration of the study. Weekends can either be included or not. If weekend days are not included the patches remain in place until Monday.

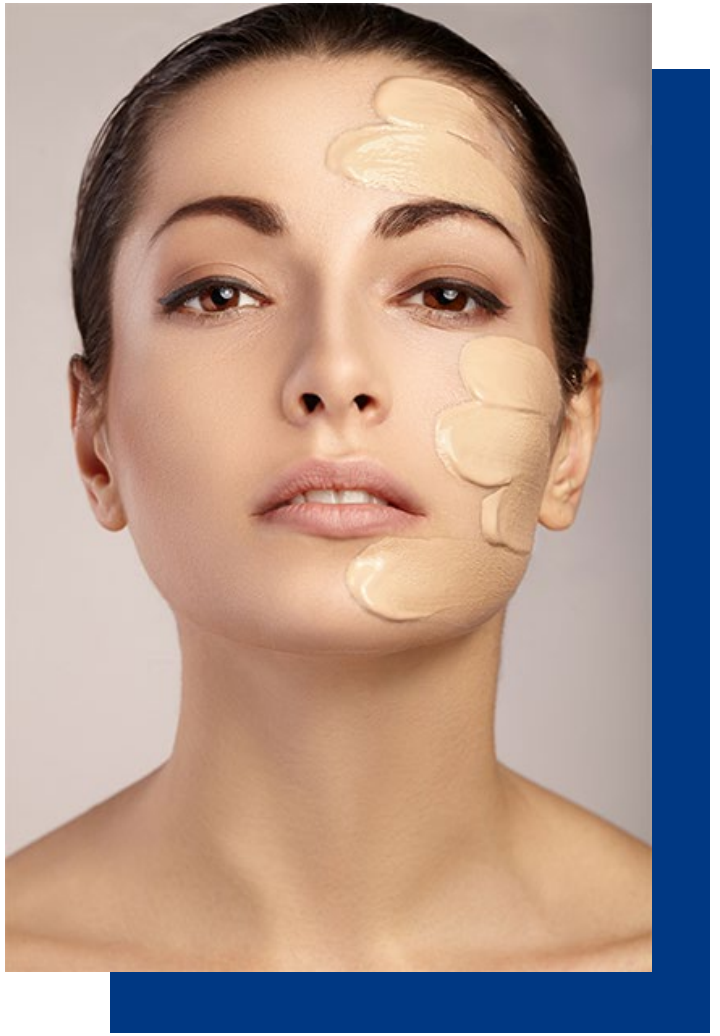
21-Day: Process is the same as the 14-day cumulative irritation but for a 21-day duration.

Sample Size:

30 subjects

Conclusion:

The total value of all reactions for a test material will be divided by the potential max score, and then multiplied by 100 to calculate the percent of max score.



Cumulative Irritation Studies (Cont.)

Conclusions continued

% of Potential Maximum Score	Conclusion
0.0%-7.8%	Essentially no evidence of cumulative irritation under conditions of test
>7.8%-31.6%	Evidence of a slight potential for very mild cumulative irritation under conditions of test
>31.6%-71.3%	Evidence of a moderate potential for mild cumulative irritation under conditions of test
>71.3%-92.1%	Evidence of a strong potential for mild-moderate cumulative irritation under conditions of test
>92.1%-100.0%	Evidence for primary irritation under conditions of test

*Cumulative irritation classifications were determined by using the same percentages of the total possible score as were used in the categorical system which appears in Berger RS and JP bowman. A reappraisal of the 21-day cumulative irritation test in man *J. Taxicol.-Cut. & Ocular Toxicol.* 1982; 1

Safety In Use Studies, When Do I Run One?

1. I have completed my RIPT and want “Real Life Use” safety testing

   - Used on an actual area of the body as in real life consumer use
   - Can perform exaggerated use studies for worst case scenario
   - I want subjects to complete a consumer perception questionnaire

OR

2. My product is not suitable for RIPT testing
   - Too harsh – ie Hair Dyes, Depilatories
   - Safety In Use replaces the RIPT for these product categories

Safety In Use Studies, What does a Typical SIU Study Look Like?

- n=35 subjects
- Baseline, Midpoint, Endpoint Evaluations
- Erythema, Edema, Dryness (basic skin evaluations, others can be added based on the product category)
- Consumer perception questionnaire can be added to gain insight about our product- Some studies are questionnaire only studies.
- These are referred to as CP or Consumer Perception studies.

How you design your SIU study should be discussed with your internal regulatory advisors. If you don't have a regulatory advisor, your 3rd party testing lab can provide guidance

Safety In Use Studies, What Types Are Performed?

- Dermatological (Face, all body parts)
- Gynecological
- Dental
- Pediatric
- Ophthalmological
- Non-Comedogenic

<u>Combination studies are also possible</u>

- Op/Derm
- Op/Derm/Comedo
- Derm/Comedo

<u>Specialized Populations</u>

- Sensitive Skin
- Acne Prone
- Contact Lens wearers
- Ethnicities

Safety In Use Studies, What Do My SIU Results Mean?

In this study population, and under the conditions of this study, the product is considered safe for use when used as directed.

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