

Rethinking Human Dermal Safety Testing for Topical Drug Products

Jonathan Wilkin, MD

FDA Human Dermal Safety Testing Workshop

September 10, 2018

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Two Types of Drug Products Intended for Use on Human Skin

- Topical Drug Products
 - _ intended to act locally at the site of application
 - _ usually applied to diseased skin (sunscreens would be an exception)
- Transdermal Drug Products
 - _ intended to act systemically
 - _ usually applied to healthy skin, often in specialized patches which help control release of the active drug (nitroglycerin ointment and other drugs in semi-solid dosage forms would be exceptions)

Provocative Testing for Local Cutaneous Adverse Events from Topical Drugs

- Irritant (toxic) contact dermatitis – “eczema” - spongiosis or intercellular edema often from direct damage to keratinocytes
- Allergic (delayed hypersensitivity) contact dermatitis (ACD)– interaction of antigen with primed T cells
- Phototoxicity – interaction of drug with 290-700 nm light to cause sunburn-like reaction - toxic
- Photoallergy – interaction of drug with 290-700nm light to cause eczematous reaction - immunologic

Human Dermal Safety Provocative Testing Battery

- Contact Irritancy Assay
- Contact Allergenicity Assay – may be combined with Contact Irritancy Assay
- Phototoxicity Assay – may be waived if no absorption in 290-700nm
- Photoallergy Assay – may be waived if no absorption in 290-700nm

Irritant Contact Dermatitis

- Due to direct toxicity from drug product
- Does not depend on immunological responses
- May demonstrate concentration relationship in early clinical trials
- Sensitization and lag periods not necessary
- May be sufficiently well-documented in clinical trials pre-Phase 3 that an additional, separate provocative irritancy test not needed

Photoallergy and Phototoxicity

- Testing is generally conducted for products with one or more ingredients absorbing in the spectrum from 290 – 700nm.
- I have not found published reports which compare post-marketing reports of adverse cutaneous events in a photo-distribution with the results of pre-marketing photodermal testing for such products. Is there evidence for the effectiveness of such pre-marketing risk assessment phototesting?

Allergic Contact Dermatitis

- Dependent on immunological sensitization and elicitation mediated by immune cells.
- May not exhibit much or any direct toxicity.
- Concentration relationship may be either not apparent or nonexistent.
- Sensitization and lag periods necessary. Allergic contact dermatitis in clinical practice is often seen after years of chronic use on diseased skin.

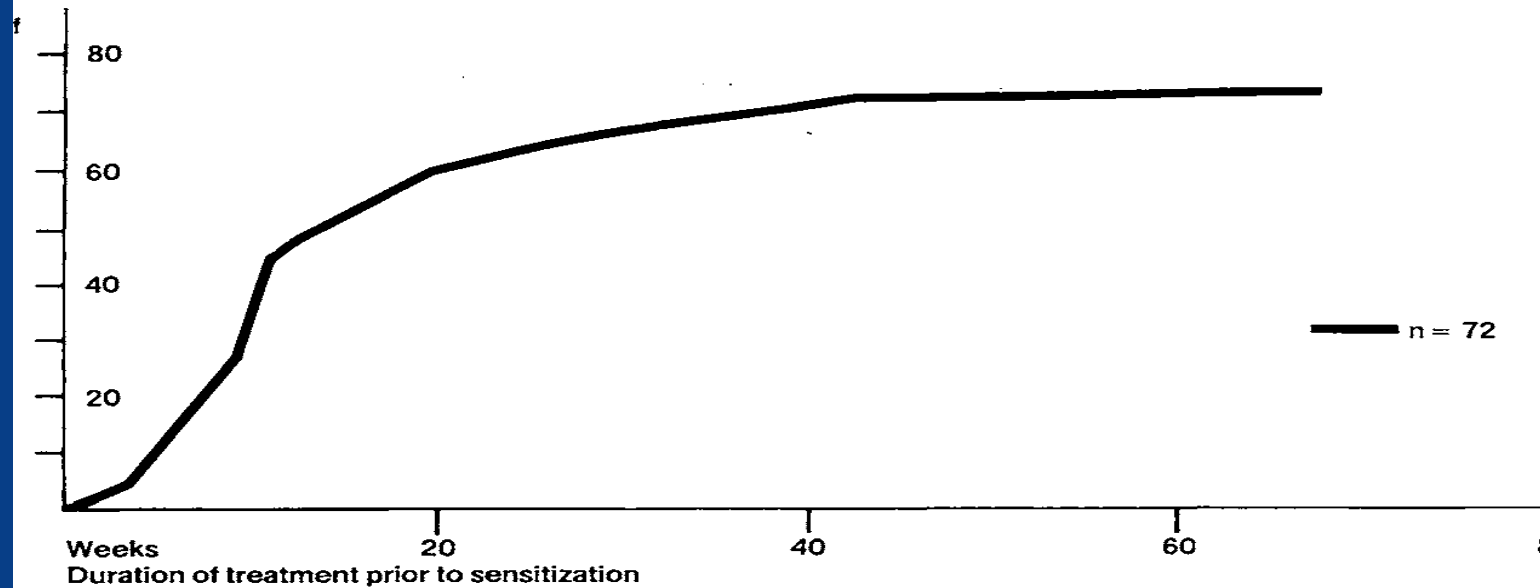
Provocative Testing for Allergic Contact Dermatitis for Topical Drug Products

- For new drug products during Phase 3 with the final to-be-marketed formulation.
- 21-day induction phase (SHORT-TERM, ACUTE testing)
- 14-17-day rest period
- Challenge phase – skin response at the patch test site is evaluated
- Enrollment of sufficient number of subjects with healthy skin to provide for 200 evaluable subjects in the per protocol population

Observations on Human Testing for Contact Allergens

- Kligman AM. J Invest Dermatol 47:375-92, 1966
- “Weaker (allergens) may be harmless for many years of intensive contact.”
- “...chemical or physical inflammation, if not too severe, increases the opportunity for contact sensitization.”

CLONIDINE:IRRITANT AND ALLERGIC CONTACT DERMATITIS ASSAYS



Relationship of treatment duration to development of contact sensitization in 72 sensitized

Clonidine: irritant and allergic contact dermatitis assays. Maibach H Contact Dermatitis 12:192-5, 1985

Delayed onset of demonstration of allergic contact sensitization in clinical trials with 90% of occurrences of allergic contact dermatitis causing discontinuation of transdermal clonidine device materializing in the first 20 weeks of treatment,

Short-term 'Acute' Sensitization Phase Testing: Could There Be a Better Way?

- The prevalence of allergic response to clonidine in transdermal products applied to skin is low in acute testing but rises to high levels after months of use.
- The phenomenon of a later onset of sensitization in products which are more irritating was described by Kligman in 1966.
- The irritancy sets up an inflammation in the skin in which cytokines and stimulating factors enhance Langerhans cell molecular biology in the induction of allergic contact dermatitis.

Population Exposure to Assess Clinical Safety for Drugs for 'Chronic' Use

- Consistent guidance: March 1995 (ICH E1A), March 2005 FDA Guidance for Industry: Pre-marketing Risk Assessment
- 'Chronic' does not mean continuous use and would include intermittent use providing for a cumulative treatment exposure that equals 6 or more months.
- Pre-marketing safety studies should include 300 to 600 evaluable subjects exposed for 6 months and 100 for 1 year, all of whom have therapeutically relevant extent and duration of exposures to the drug product.

Could Chronic Safety Studies Inform Risk for Allergic Contact Dermatitis?

- Use product as labeled for 6 months and 1 year as part of the already requested (since 1995) pre-marketing risk assessment for chronic use products.
- Would allow for detecting allergic contact dermatitis with induction periods longer than 21 days, on sites with active skin disease, and over areas much larger than the current test patch.
- No vehicle control; and, duration, volume and area of exposure would be variable even within individual subjects.

Evaluating Risk for Allergic Contact Dermatitis in Chronic Safety Studies

- Would require pre-specification of the combination of signs and symptoms which would trigger the resting and challenge phases.
- Planimetric areas of involved skin and container weights may be monitored to estimate amount of product consumed.
- Local IRBs may address incentivization in an ethically acceptable manner to encourage participation in the challenge phase to enhance the evaluation population and the scientific and public health value of the study.

“Label-worthy” Information

- Truth is necessary, but may be insufficient.
- “Label-worthy” is information that is both true and is relevant for using the product safely and effectively (21CFR201.56).
- Adding the characterization of potential ACD to the chronic use studies should provide “label-worthy” information not provided by the current acute patch testing method.

“Label-worthy” ACD Information from Chronic Safety Studies

- Information on the frequency of ACD in subjects in the indication population instead of only subjects with healthy skin.
- Information on the time of onset and time course of ACD.
- Information on severity of ACD, including effect of the ACD on the indicated condition, usually a specific dermatosis or group of dermatoses.

Evaluation of Risk for ACD in Products Intended for Less Than Chronic Use?

- Use current patch testing and **state clearly in labeling** that ACD sensitization has not been evaluated for periods of exposure longer than 21 days, and
- Consider a post-marketing commitment to complete an already initiated 6 month chronic safety study in which the potential for ACD is evaluated.

Employ Current Sensitization Patch Testing Method for Important Uses

- Early clinical studies of a topical product which contains a novel inactive ingredient.
- Early clinical studies of a topical product for which the active ingredient is in an approved, systemically delivered product which is uniquely effective for a serious medical condition (risking the 'baboon syndrome': systemically-induced allergic contact dermatitis. Andersen KE, et al. Contact Dermatitis 10:97-100, 1984; Hausermann P, et al., Contact Dermatitis 51:297-310, 2004).
- Consider for early clinical studies of a topical product which contains a NME and is being developed for a non-serious medical condition.

Consider Empiric Data & Rethink Human Dermal Safety Test Methods I

- Irritant Contact Dermatitis – topically applied products may have sufficient empiric data by the End-of-Phase 2 Meeting to indicate that the Phase 3 efficacy and safety studies should sufficiently inform the potential for irritancy under labeled use conditions on diseased skin.
- Photoallergenicity/Phototoxicity – there may now be sufficient durations of post-marketing experience for topical products for which phototesting studies were submitted to FDA which may provide insights into the usefulness of such pre-marketing phototesting studies.

Consider Empiric Data & Rethink Human Dermal Safety Test Methods II

- Allergic Contact Dermatitis – topical products may generate higher frequencies of ACD **later** compared to frequencies demonstrable in the current ‘acute’ patch testing method (e.g., clonidine).
- Switching the demonstration of the potential for ACD to the currently recommended pre-marketing chronic clinical safety studies may provide less precise, but more relevant, ‘label-worthy’ information.

Human Dermal Safety Tests: Replacement, Reduction & Refinement

- Given the current guidance for chronic human safety studies, consider whether such studies may be modified for topical products to sufficiently assess:
 - 1) both photoallergenicity and phototoxicity potentials, allowing for the elimination of the photo-patch testing in some Phase 3 clinical development programs.
 - 2) both irritancy and allergic potentials, allowing for the elimination of the acute patch testing in some Phase 3 clinical development programs.

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