Integrated Safety Testing and Assessment of Topical Drug Products

Human Dermal Safety Testing for Topical Drug Products
FDA Public Workshop

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Outline

I. Summary and Conclusion
II. Photosafety testing
III. Skin irritation testing
IV. Skin sensitization testing
V. References
Summary and Conclusion

• Assessment of photosafety, skin irritation and skin sensitization potential have integrated testing approaches built from an understanding of adverse outcome pathways (AOP).

• Mechanistic-based dermal toxicity testing has been designed to improve predictivity of adverse events in humans following topical product application.

• Collaboration amongst academics, industry, regulatory authorities and nongovernmental organizations have helped progress such testing approaches and criteria used to assess adverse outcomes.
II. Photosafety Testing

• Physiochemical properties: UV/visible light absorption
  – Bauer et al. (2014): “A molar extinction coefficient (MEC) of 1000 L mol\(^{-1}\) cm\(^{-1}\) has been confirmed as a reliable and sensitive threshold in order to identify compounds that absorb light of 290-700 nm.
    • If MEC < 1000 L mol\(^{-1}\) cm\(^{-1}\), no further testing

• In vitro Testing
  – Epidermis models, e.g., Episkin, phototoxicity testing, i.e., insoluble, finished formulae
    • If “negative” outcome, no further testing is needed. If “positive”, next step is in vivo testing.

• In vivo Testing
  – Preclinical (for review preclinical models see: Spielmann et al. 2000; Nash, 2009)
    • Photoirritation (ingredient or formulation)
    • Photoallergy (ingredient or formulation)
  – Human Clinical Testing
    • Confirmatory phototoxicity/photoirritation—formulation: Kaidbey and Kligman (1978)
    • Confirmatory Photoallergy—formulation: Kaidbey and Kligman (1980)

• Clinical Trials
  – Risk assessment and minimization, e.g., light avoidance
  – Biomarkers
    • Noninvasive: erythema, pigment changes
    • Invasive: histopathology, e.g., “sunburn” cells
Figure 1: Outline of Possible Phototoxicity Assessment Strategies for Pharmaceuticals Given via Systemic and Dermal Routes

Initial Assessment of Phototoxic Potential
- UV-vis spectrum in melanin (290 – 700 nm)
  - MEC < 1000 L/mol cm
  - Optional
- MEC > 1000 L/mol cm
- Chemical photoreactivity assay
  - "negative"
  - No further phototoxicity testing
  - No light protective measures in clinical trials
  - Otherwise *

Experimental Evaluation of Phototoxicity Options for collecting additional data in biological systems
- In vitro phototoxicity test
- Distribution to light-exposed tissues 2
- In vivo preclinical phototoxicity test
- Clinical evaluation 3
  - "negative"
  - Clinical: In vivo + in vitro
  - Otherwise *

Determine adequate risk minimization measures to prevent adverse events in humans

* "otherwise": data do not support a low potential for phototoxicity or have not been generated (assay/less/evaluation not conducted)

2 A "negative" result in an appropriately conducted in vivo phototoxicity study supercedes a positive in vitro result. A robust clinical phototoxicity assessment indicating no concern supercedes any positive non-clinical results. A positive result in an in-vivo phototoxicity test could also, on a case-by-case basis, be negated by tissue distribution data (see text). In the United States, for products applied dermally, a dedicated clinical trial for phototoxicity on the to-be-marketed formulation can be warranted in support of product approval.

3 Clinical evaluation could range from standard reporting of adverse events in clinical studies to a dedicated clinical photosafety trial.

4 Tissue distribution is not a consideration for the phototoxicity of dermal products.
III. Skin Irritation: Testing*

- Physicochemical properties
  - e.g., pH, acid/alkaline reserve, oxidants, exothermic
- In silico
  - (Q)SAR, read-across, expert rules-based systems, e.g., DEREK, TOPKAT
- In vitro
  - OECD 430, 431 & 435: In vitro skin corrosion testing
  - OECD 439: In vitro skin irritation: reconstructed human epidermis (RHE) test method.
- In vivo
  - Preclinical
    - OECD 404 Acute dermal irritation/corrosion
  - Human Clinical Testing:
    - Confirmatory formulation testing: Acute (3, 24 or 48 hr) and/or cumulative (4 – 21 day) irritation patch test
- Clinical Trials
  - Biomarkers
    - Noninvasive: IL-1α, IL-1ra
    - Invasive: histological evidence of inflammation

IV. Skin Irritation: Testing

- Integrated Approach on Testing and Assessment (IATA) modules
- Application possible for formulations
IV. Skin Sensitization: Testing

- **Physicochemical Assessment**
  - Log P (oil/water partition coefficient), pKa, Wat solubility etc.

- **In silico**
  - Structural alerts, (Q)SAR, read-across, expert rules-based systems, e.g., DEREK, TOPKAT, TIMES etc.

- **In chemico**
  - Direct Protein Reactivity Assay (DPRA) – OECD TG 442c. Screening method for evaluation of skin sensitization potential (haptens, prehaptens)

- **In vitro**
  - Keratinocyte response: ARE-Nrf2 Luciferase Test Method KeratinoSens™ - OECD TG 442d
  - Dendritic cell response: h-CLAT (Human Cell Line Activation Test) – OECD TG 442e

- **In vivo**
  - Preclinical: Local lymph node assay (LLNA) – OECD 429
  - Human: Repeat Insult Patch Testing (HRIPT) – Formulation testing. Confirmatory

- **Clinical Trials**
  - Formulation testing
  - No established biomarker

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IV. Skin Sensitization: AOP

V. References: Photosafety


V. References: Skin Irritation


OECD 2010. Test No. 439: In Vitro Skin Irritation.


*EPISKIN™, EpiDerm™, and SkinEthic™ accepted by US via OECD guideline 439
V. References: Skin Sensitization


OECD 2010. Test No. 429: Skin Sensitisation.

OECD 2014. The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins.

OECD 2015. Test No. 442C: In Chemico Skin Sensitisation.


OECD 2017. Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation. No. 256

OECD 2018a. Test No. 442D: In Vitro Skin Sensitisation.

OECD 2018b. Test No. 442E: In Vitro Skin Sensitisation.