Nonclinical Aspects of Dermal Safety Testing

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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

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Nonclinical Studies for Assessing Dermal Safety of Topical Drug Products

- Dermal irritation studies
- Dermal sensitization studies
- Ocular irritation studies
- Dermal photosafety studies

Dermal Irritation

- Stand-alone dermal irritation studies are no longer recommended because such information can be obtained from other studies; This also supports implementation of the 3Rs (replacement, reduction and refinement of animal use)
- Recommend evaluation of dermal irritation be incorporated into repeat-dose dermal toxicology studies (typically minipigs)
- In vitro assays used as screen for in vivo

Dermal Sensitization

- A dermal sensitization study in guinea pigs, using clinical formulation
- The murine Local Lymph Node Assay (LLNA) is no longer recommended due to limitations of the assay (high false positive rate)
  - We will review a submitted LLNA for a topical drug product and accept the outcome particularly if the result is negative
- In vitro assays used as screen for in vivo
  - A battery of tests with different endpoints

Ocular Irritation

- The in vivo rabbit ocular irritation test is no longer recommended
- The ocular irritation potential should be tested using appropriate ex vivo or in vitro methods
- The bovine corneal opacity and permeability (BCOP) assay is currently recommended
  - The evaluation should consider the active ingredient and the finished formulation
- Dermal irritant is assumed to be ocular irritant
  - No test needed

Photosafety Introduction

- ICH S10 guidance (January 2015)
  - *Photosafety Evaluation of Pharmaceuticals*
- Effects related to Photosafety
  - Phototoxicity (photoirritation): An acute light-induced tissue response to a photoreactive chemical
  - Photoallergy: An immunologically mediated reaction to a chemical, initiated by the formation of photoproducts (e.g., protein adducts) following a photochemical reaction

Nonclinical Photosafety Assessment

- Focus on nonclinical photosafety assessment for topical drug products applied to sun exposed skin
- In vitro nonclinical phototoxicity assessment
- In vivo nonclinical phototoxicity assessment
- A photoallergy study in animals is not recommended
  - Not predictive of clinical effects
- Photogenotoxicity and photocarcinogenicity testing is not recommended
  - Not predictive of clinical effects

Photochemical Properties

- Absorption of photons at any wavelength between 290 and 700 nm
- Has a molar extinction coefficient (MEC) greater than 1000 mol^{-1} cm^{-1} at any wavelength between 290 and 700 nm
- If either condition is not met, then not considered to be sufficiently photoreactive to result in direct phototoxicity
- No further nonclinical or clinical testing required

Photochemical Reactivity

- Excitation by light can lead to generation of reactive oxygen species (ROS)
  - Superoxide anion and singlet oxygen
- ROS generation following irradiation with UV-visible light (i.e., wavelength between 290 and 700 nm) can be an indicator of phototoxicity potential

Nonclinical Phototoxicity Studies In Vitro

- 3T3 Neutral Red uptake assay (cytotoxicity assay)
  - For soluble compounds, most widely used
  - High false positive rate
  - If negative, then no concern; If positive, then follow-up
- ROS assay (chemical assay)
  - ROS assay is qualified for certain contexts of use
  - Limitations must be taken into consideration
  - High false positive rate
- Other in vitro models (e.g., human skin models)
  - Not many submitted

Decision Tree for in Vitro Nonclinical Phototoxicity Studies

- Absorption at any wavelength between 290 and 700 nm with a MEC greater than 1000 mol^{-1} cm^{-1}
- Conduct 3T3 Neutral Red uptake assay
- Negative – No further nonclinical testing, inform clinical review team
- Positive – Follow up in vivo nonclinical testing

Nonclinical Phototoxicity Studies In Vivo

- Acceptable animal species: mouse, rat, guinea pig
- Apply clinical formulation to the skin followed by simulated solar light exposure
- Signs of phototoxicity should be evaluated based on relevant endpoints at appropriate timepoints
  - Erythema, edema, eschar at the treatment site
  - Evaluated over hours to days

Decision Tree for in Vivo Nonclinical Phototoxicity Studies

- Absorption at any wavelength between 290 and 700 nm with a MEC greater than 1000 mol^{-1} cm^{-1}
- Conduct in vivo animal phototoxicity study
- Negative or Positive – No further nonclinical testing, inform clinical review team

Positive Nonclinical Phototoxicity Reactions

- Inform subjects in Investigator's Brochure/ Informed Consent
- Photosafety testing in human clinical studies with the to-be-marketed formulation
- Labeling should include a precaution to avoid sun exposure

Negative Nonclinical Phototoxicity Reactions

- No information for subjects in Investigator's Brochure/Informed Consent
- In US, photosafety testing in human clinical studies with the to-be-marketed formulation
- Information in labeling depends on results of clinical photosafety studies

Questions?