TIERED TESTING STRATEGY USING VALIDATED *IN VITRO* ASSAYS FOR THE ASSESSMENT OF SKIN AND EYE CORROSION/IRRITATION OF PHARMACEUTICAL INTERMEDIATES

Calufetti, Susan[1]; Nelson, Kimberly O.[1]; Costin, Gertrude-Emilia[2]; Krcha, Monica[2]; Wilt, Nathan[2]

1. Eli Lilly and Company, Indianapolis, IN, U.S.A.
2. Institute for In Vitro Sciences, Inc. (IIVS), Gaithersburg, MD, U.S.A.

ABSTRACT

The safety of workers handling solid pharmaceutical intermediates was assessed using a tiered testing strategy based on regulatory validated *in vitro* assays. The Top-Down approach was initiated with the *in vitro* skin corrosion assay (OECD TG 431) followed by the *in vitro* skin irritation assay (OECD TG 439) using the reconstructed human epidermis model from MatTek Corporation. Of the ten pharmaceutical intermediates tested, nine were predicted to be non-corrosive to skin and were subsequently confirmed as non-irritants. The only intermediate predicted corrosive to skin was further tested using the Corrositex® assay (OECD TG 435) and was assigned a corrosive packing group II classification. Furthermore, three intermediates predicted non-corrosive/non-irritant to skin were tested as 20% dilutions in water in the *in vitro* Bovine Corneal Opacity and Permeability (BCOP) assay (OECD TG 437) and they were predicted as non-irritants to the eye. Our tiered skin and eye corrosion/irritation testing strategy proved to be a very useful platform for the assessment of the potential safety risk posed to workers during the manufacturing operations used for pharmaceutical intermediates.

INTRODUCTION

Advances in the field of *in vitro* toxicology allow for fast and reliable pre-clinical safety testing of a large variety of raw ingredients and final formulations produced by various industries. As such, the safety profile of pharmaceutical intermediates can be assessed by employing a tiered testing strategy that best addresses the goals of the manufacturer. In our study, a series of solid pharmaceutical intermediates were tested for skin and eye corrosion/irritation with the final goal of confirming their safety when handled for transportation or other purposes. Beyond the initial goal of assessing the safety of the intermediates, we established a working tiered testing strategy. The strategy is initiated with skin corrosion testing and is followed up by skin irritation testing if a non-corrosive prediction is obtained. If a corrosive prediction is obtained, the Corrositex® assay can then be used to obtain a packing group classification. Ocular corrosion/irritation testing is also conducted to complete the safety assessment. This testing strategy is a reliable pre-screening tool with wide applicability in industry for the purpose of safety profiling of intermediates or final products.

RESULTS

- 10 materials were tested in the EpiDerm™ Corrosion Assay (OECD TG 431) for 3 and 60 minutes.
- 9 of 10 materials were subsequently confirmed as non-irritants in the EpiDerm™ Skin Irritation Assay (OECD TG 439). The remaining material was predicted to be corrosive, and was further tested in the Corrositex Assay (OECD TG 435) and assigned a packing group II classification.
- 3 of 10 materials were further tested as 20% dilutions in water for 4 hours in the Bovine Corneal Opacity and Permeability (BCOP) Assay (OECD TG 437) and were predicted as non-irritating to the eye.

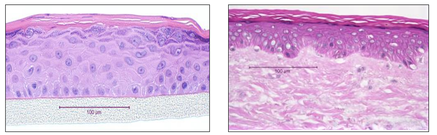
***IN VITRO* ASSAYS PERFORMED FOR SAFETY ASSESSMENT OF PHARMACEUTICAL INTERMEDIATES**

Pharmaceutical Intermediate	Skin Corrosion Assay	Skin Irritation Assay	Corrositex Assay	BCOP Assay	
	Result			*In vitro* Score	Result
1	Non-corrosive	Non-irritant			
2	Non-corrosive	Non-irritant			
3	Corrosive		Packing Group II		
4	Non-corrosive	Non-irritant			
5	Non-corrosive	Non-irritant			
6	Non-corrosive	Non-irritant			
7	Non-corrosive	Non-irritant			
8	Non-corrosive	Non-irritant		3.2	Non-irritant
9	Non-corrosive	Non-irritant		-0.8	Non-irritant
10	Non-corrosive	Non-irritant		-1.0	Non-irritant

MATERIALS & METHODS

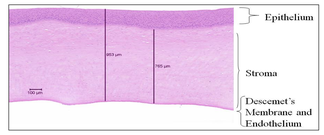
- **Test materials**: Solid pharmaceutical intermediates
- **Test systems**: the EpiDerm™ model (MatTek Corporation), bovine corneas, and Corrositex® membrane discs
- ***In vitro* assays**:
  - Skin Corrosion Assay (OECD TG 431) and Skin Irritation Assay (OECD TG 439) using the EpiDerm™ model from MatTek Corporation (**Figure 1 – only Skin Irritation Assay displayed**)
  - Bovine Corneal Opacity and Permeability Assay (OECD TG 437) (**Figure 2**)
  - Corrositex® Assay (OECD TG 435) (**Figure 3**)
- **Prediction models**:
  - **Table 1a**: skin corrosion
  - **Table 1b**: skin irritation
  - **Table 2**: eye corrosion/irritation
  - **Table 3**: Corrositex®

Structural architecture of the EpiDerm™ tissue model and native human skin



EpiDerm™ Tissue Model | Native Human Skin

Structural architecture of the bovine cornea



Native Bovine Cornea

Figure 1: Outline of the Skin Irritation Assay

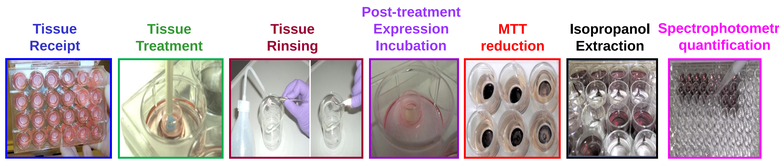


Figure 2: Outline of the Bovine Corneal and Opacity (BCOP) assay

Figure 3: Outline of the Corrositex® assay

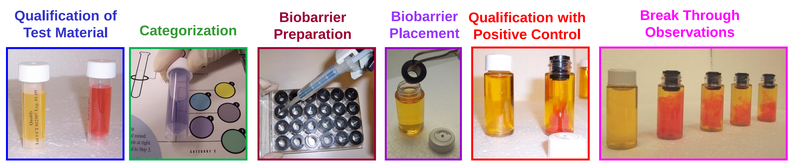


Table 1a: prediction model for skin corrosion

Mean Tissue Viability	Prediction to be considered UN GHS Category	
< 50% after 3 minute exposure	Corrosive	1A
≥ 50% after 3 minute exposure and <15% after 60 minute exposure	Corrosive	1B/1C
≥ 50% after 3 minute exposure and ≥ 15% after 60 minute exposure	Non-corrosive	Non-corrosive

Table 1b: prediction model for skin irritation

Mean Tissue Viability	Prediction to be considered UN GHS Category	
< 50%	Irritant	Category 2
≥ 50%	Non-irritant	No Category

Table 2: prediction model for eye corrosion/irritation

In Vitro Score	
0 to 4	Non-irritant
4.1 to 12	Slight irritant
12.1 to 25	Mild irritant
25.1 to 55	Moderate irritant
55.1 and above	Severe irritant

***In Vitro* Score = Mean Opacity Value + (15 x Mean OD_{490} Value)**

Classifications developed based on and modified from Gautheron et al., 1992 (Sina scale) for the specific testing needs of pharmaceutical intermediates manufactured by Eli Lilly and Company.

Table 3: prediction model for packing groups

Category I

Mean Time to Produce a Change in Chemical Detection System	Packing Group
≤ 3 Minutes	I
> 3 Minutes - 1 Hour	II
> 1 - 4 Hours	III
> 4 Hours	Not Applicable

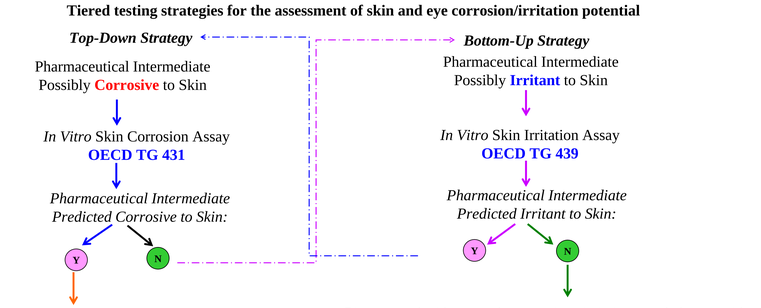
Corrosivity
Corrosive
Corrosive
Corrosive
Non-corrosive

Category II

Mean Time to Produce a Change in Chemical Detection System	Packing Group
≤ 3 Minutes	I
> 3 Minutes - 30 minutes	II
> 30 - 60 minutes	III
> 60 minutes	Not Applicable

CONCLUSIONS

Tiered testing strategies for the assessment of skin and eye corrosion/irritation potential



- Pharmaceutical intermediate may be labeled as corrosive to skin.
- Pharmaceutical intermediate may also be classified by the relevant packing group: Corrositex Assay (OECD TG 435).
- Pharmaceutical intermediate may be labeled as non-irritant to skin.
- Pharmaceutical intermediate may also be further tested for eye irritation using the BCOP Assay (OECD TG 437).

REFERENCES

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