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 vivo 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-corrrosive 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-corrrosive to skin were tested as 20% dilutions in water for 4 hours in the Bovine Corneal Opaquity 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 with an eye irritation assay 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 Corrosion Test Method (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.

CONCLUSIONS

- 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)
    - Corrosion Test Method (OECD TG 435) (Figure 3)
- Prediction models:
  - Table 1a: skin corrosion
  - Table 1b: skin irritation
  - Table 2: eye corrosion/irritation
  - Table 3: Corrosivity

REFERENCES