

## Summary Minutes

### PQRI-PODP Toxicology Sub-Team Working Group Meeting – 26JAN2010

Location: Forest Laboratories, Jersey City, NJ

-Admonition statement was acknowledged.

#### -Cramer Classification

- ToxTree Cramer Classification was demonstrated via web.
- 606 compounds were evaluated by Cramer criteria alone and using -
- Overall exercise indicated that Cramer classification is intrinsically conservative.

-Group Discussion related to AET and Cramer classification relative to extractable studies.

#### -Toxicology Classification

- discussed the draft thresholds determined based on Cramer classifications and thresholds.
- Group discussed applicability and considerations specific to ophthalmic drug products (i.e. concentration and volume concerns).
- Table was drafted and draft thresholds were included as a starting point, as follows:

Class	1	2	3	Sensitizer	Irritant	Genotoxicant
Threshold dose for non-ophthalmics	150 µg/day	45 µg/day	7.5 µg/day	-	-	0.15 µg/day
Threshold dose for ophthalmics	<b>Option 1 (unlikely)</b>			<b>Option 2 (more likely)</b>		
	15 µg/day	4.5 µg/day	0.75 µg/day	0.5 µg/day	0.5 µg/day	0.15 µg/day
N-Nitrosodiethylamine <sup>d</sup>						
Acenaphthene			√			
Methylbutyl ketone		√				
Methyl methacrylate*			√			
1-undecene	√					

L&E classification are modified Cramer based on:

a. 50 kg person

b. Threshold dose for non-ophthalmics: Additional 10x safety factor (total factor of 1,000) to account for route of administration (IV).

c. Threshold dose for ophthalmics: Option 1: Additional 10x safety factor (total factor of 10,000) for route of administration (ophthalmic) (UNLIKELY); Option 2: Sensitizer/Irritant = ophthalmic class for all non genotoxicants (Class 1-3 chemicals) are qualified at 0.5 µg/day or 0.15 µg/day (genotoxicant) (LIKELY).

d. Special cases (PNAs, NAs and MBT) are excluded from this classification and will need to be assessed on a case-by-case basis.

e. LVP require analytical considerations as an additional assessment filter to account analytical LOD/LOQ.

\*reclassified based on a literature based assessment

Next Steps-

-Briefing document and slide deck to be prepared for FDA

Briefing Book outline was described as follows:

-Executive Summary (1/2 page)

-Questions (approx 5)

-Overview/Background on Cramer, use in PQRI OINDP (1-1.5 pp)

-Application of in silico approaches to Leachables and Extractables for  
PODP (2 pp)

-Text and Table with Proposals and Caveats (2 pp)

-Next Steps (0.5-2 pp)

-Conclusions

Meetings with FDA and Health Canada targeted for end-March.

Next Toxicology sub-team telecom targeted for first week in March.