**November 4, 2019 Workshop Questions**

(Please note that Question 1 is generally intended to be the overriding question for the workshop):

1. How many doses of an Ames-positive drug (DNA reactive drug) can be safely administered to Healthy Subjects?

- 1, 2, 3, or 4 doses

2. If studies in healthy subjects are acceptable with a mutagenic drug, how should such studies be designed?

a) Is continuous daily dosing acceptable? If so, for how long?

b) If dosing is intermittent, how many doses would be acceptable?

3. For generic drug products, the results of the full battery of genetic toxicology and carcinogenicity studies are often stated in the Reference Listed Drug's label. Should a weight-of-evidence approach be used to decide whether a compound should be tested in bioequivalence studies with healthy subjects?

a) If yes, which test results should receive greatest consideration in the WOE assessment?

b) Are there any other factors relating to genetic toxicology that should be considered when determining if a study should include healthy subjects in bioequivalence studies?

4. Certain drugs may be clastogenic, but not mutagenic. Should consideration be given to the mechanism of action of genotoxicity in designing studies in healthy subjects?

5. The ICH S2 (R1) Guidance provides recommendations for follow-up to a positive in vitro mammalian cell clastogenicity assay. If a drug is mutagenic (Ames-positive; artifactual increases have been excluded), are there follow-up studies to assess risk that should be conducted prior to conducting studies in healthy volunteers?

a) Would a 28-day transgenic rodent mutation assay that includes a Pig-a endpoint be acceptable? (If the Pig-a endpoint is positive, there would be no need to proceed with the tissue analysis in the TRG assay. However, if the Pig-a endpoint is negative, the tissue evaluation should proceed)

b) Alternatively, should a 26-week TgrasH2 mouse carcinogenicity assay or a 2-year rodent carcinogenicity study be requested?

6. Can you provide guidance for a path-forward for development of a DNA-reactive drug?

a) Mechanism of action

b) Structural considerations (e.g., functional groups on the molecule)

c) Read-across comparisons to similar molecules with known safety information

d) Observed genotoxic response (e.g., mutation, clastogenic, aneugenic)

e) Follow-up assays as described in Question 6 (e.g., alternative in vivo gene mutation test or two-year rodent bioassay).

f) Allow microdosing of such drug without any follow up assessment.

7. Are there drug classes or specific drugs (e.g., targeted to the epigenome) that should never be administered to Healthy Subjects?