Discussion Points for Panel Discussion

Genotoxicity studies

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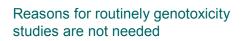
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ICH guidelines for genotoxicity studies

- S2A: Guidance on specific aspects of regulatory genotoxicity tests
- S2B: Genotoxicity : A standard battery for genotoxicity testing of pharmaceuticals
- There is no description for biopharmaceuticals or proteins (peptides) in both guidelines



 The range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

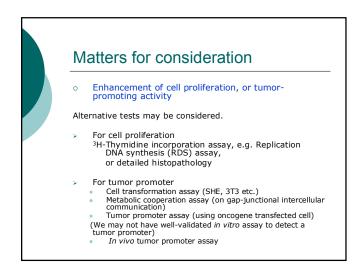


 Proteins and peptides are not expected to interact directly with DNA or other chromosomal material by passing through the cell or nuclear membranes.

Reasons for standard genotoxicity studies are not needed (cont.)

 There is a potential concern about accumulation of spontaneously mutated cells (e.g., via facilitating a selective advantage of proliferation) leading to carcinogenicity.

However, the standard battery of genotoxicity tests is not designed to detect these conditions.



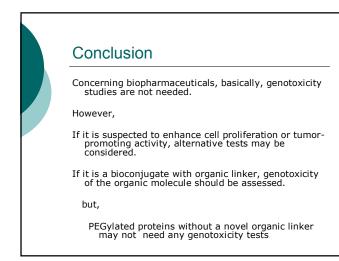


\circ Bioconjugates with organic linker

- Genotoxicity of the organic molecule should be assessed.
- Routinely studies are conducted under conditions in which derivatives of the organic molecule are generated.
- The organic molecule are directly tested in routinely studies.

How about PEGylated proteins?

Any genotoxicity studies for PEGulated proteins without a novel organic linker may not be needed, because a safety of PEGs has been sufficiently evaluated and a polymer, such as PEG, does not pass through the cell or nuclear membranes



	Genotoxicity studies performed for biopharmaceuticals approved in Japan (2001 - 2006)							
	No. of substances	Bacteria Mutation	Mammalian cell Chrom. Abb.	Rodent Micronuclei	Mammalian cell Mutation	Rodent UDS	Not Done]
	22	16	16	11	6	2	6	1
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