Discussion Points for Panel Discussion

Genotoxicity studies

Akihiro Wakata
(Astellas Pharma Inc.)

August 10, 2007

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

Genotoxicity studies in ICH S6 guideline

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

Reasons for routinely genotoxicity studies 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.

Matters for consideration

- Enhancement of cell proliferation, or tumor-promoting activity

Alternative tests may be considered.

- For cell proliferation
  - ^{3}H-Thymidine incorporation assay, e.g. Replication DNA synthesis (RDS) assay, or detailed histopathology
- For tumor promoter
  - Cell transformation assay (SHE, 3T3 etc.)
  - Metabolic cooperation assay (on gap-junctional intercellular communication)
  - Tumor promoter assay (using oncogene transfected cell)

  (We may not have well-validated *in vitro* assay to detect a tumor promoter)
  - *In vivo* tumor promoter assay

Matters for consideration (cont.)

- 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

Conclusion

Concerning biopharmaceuticals, basically, genotoxicity studies are not needed.

However,

If it is suspected to enhance cell proliferation or tumor-promoting activity, alternative tests may be considered.

If it is a bioconjugate with organic linker, genotoxicity of the organic molecule should be assessed.

but,

PEGylated proteins without a novel organic linker may not need any genotoxicity tests

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