S2(R1)

Revision of the Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

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International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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Revision of ICH S2A + S2B = S2R1

- S2A: Specific Aspects of Regulatory Genotoxicity Tests (1995)
- S2B: A Standard Battery for Genotoxicity Testing (1997)
- S2(R1): Guidance on Genotoxicity Testing and Data Interpretation
  - First EWG meeting in October 2006

Reasons for Revision

- high rate of (false) positive findings in *in vitro* mammalian cell tests

- better consideration of new test methods
  - in vitro micronucleus test
  - in vivo models applicable to a variety of tissues
  - use of rat blood for micronucleus evaluation

- further improvement of animal welfare aspects (“Three Rs“)

Summary of major revisions

- *In vitro* mammalian cell assay
  - Top concentration: reduced from 10 to 1 mM
  - Cytotoxicity limits: more clearly defined
  - Testing of precipitating concentrations: no longer required
- *In vitro* bacterial mutation assay no longer requires duplicate assay

Summary of major revisions

Follow-up strategy for *in vitro* positives

positive result in mammalian cell assay
(insufficient weight of evidence to indicate lack of relevance)

either

***in vitro* studies to provide <u>mechanistic information</u>**

or

two appropriate *in vivo* assays,
usually with different tissues,
and with supporting demonstration of exposure

Summary of major revisions

- Advice on choice of 2. *in vivo* genotoxicity endpoint (e.g. follow-up testing)
  - includes Comet assay, decrease emphasis on UDS assay
- Integration of genotoxicity endpoints into routine repeat dose toxicity studies
  - Stringent criteria defined for acceptability of top dose

Revised testing battery: 2 Options!

Current (S2B)	Revised S2	
	Option 1	**Option 2**
Bacterial gene mutation (with repeat)	**Bacterial gene mutation** **(no repeat)**	**Bacterial gene mutation** **(no repeat)**
In vitro mammalian cell test: Chromosome aberrations OR: mouse lymphoma assay ➔ 10 mM top conc ➔ > 50/80 % cyotoxicity	**In vitro mammalian cell test:** **Chromosome aberrations** **OR: mouse lymphoma assay** **OR: micronucleus assay** ➔ **1 mM top conc** ➔ **at most 50/80 % cytotoxicity**	**NO in vitro assay in mammalian cells!**
In vivo micronucleus test (acute stand alone test)	**In vivo micronucleus test** **(preferably integrated into rodent toxicity study)**	**In vivo micronucleus test** **2nd in vivo endpoint/tissue** **(preferably integrated into rodent toxicity study)**

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Dose acceptance criteria in general toxicity study for genotoxicity evaluation

- Maximum feasible dose
- Limit dose (1000 mg/kg for ≥ 14 days)
- Maximal possible exposure:
  - plateau/saturation in exposure
  - compound accumulation
- Top dose is ≥ 50% of top dose that would be used for acute administration

Benefits of revisions

- Incorporates accumulated knowledge specific to testing of pharmaceuticals
- Takes advantage of new technologies
- More options in the test battery
- Reduction in delays caused by dealing with “non-relevant” *in vitro* positives
- More efficient use of resources

Benefits of revisions: The 3 R's

- No concurrent positive controls in every *in vivo* assay
- Genotoxicity integrated into existing tox studies
- Incorporation of 2 genotoxicity assays in one study using the same animals
- Reduction in "non-relevant" *in vitro* results = less follow-up *in vivo* assays

Current status

- Discussion of regional consultation comments (Step 3) completed (June 08)
  - unsolved issue: feasibility of integration of endpoints into repeat dose toxicity study
  - industry collaborative study ongoing
- Step 4 Expert Document expected in June 2009 (Yokohama)

ICH S2 Expert Working Group plus observers

Health Authorities

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