# S2(R1)

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

Peter Kasper – BfArM and S2(R1)EWP



### 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**

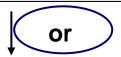
Follow-up strategy for in vitro positives

#### positive result in mammalian cell assay

(insufficient weight of evidence to indicate lack of relevance)



in vitro studies to provide mechanistic information



#### 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	In vitro mammalian cell test: Chromosome aberrations OR: mouse lymphoma assay OR: micronucleus assay	NO in vitro assay in mammalian cells!	
<ul><li>→ 10 mM top conc</li><li>→ &gt; 50/80 % cyotoxicity</li></ul>	→ 1 mM top conc → at most 50/80 % cytotoxicity		
In vivo micronucleus test	In vivo micronucleus test	In vivo micronucleus test  2 <sup>nd</sup> in vivo endpoint/tissue	
(acute stand alone test)	(preferably integrated into rodent toxicity study)	(preferably integrated into rodent toxicity study)	



# 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	<u>Industry</u>
--------------------	-----------------

MHLW	<b>Makoto Hayashi</b> (Chair), NIHS Masamitsu Honma, NIHS	JPMA	Akihiro Wakata, Astellas Pharma Shigeki Sawada, Eisai Co
EU	Peter Kasper, BfArM (D) J. W. van der Laan, RIVM (NL)	EFPIA	Hiroyasu Shimada, Daiichi Pharma <b>Lutz Müller</b> , F. Hoffmann-La Roche Veronique Thybaud, Sanofi-aventis
FDA	<b>David Jacobson-Kram</b> , CDER Tim Robison, CDER	PhRMA	<b>Jerry D. Frantz</b> , BMS Sheila M. Galloway, Merck

