RSESS SOT 2010 “Great Debate”

Are the Blind Leading the Blind or Are Pathologists Biased?

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A Debate on the Pros and Cons of Blinded Histopathology Evaluation for the Qualification of New Biomarkers of Toxicity

Speakers:

Karamjeet Pandher BVSc, PhD, DACVP – Dept of Toxicologic Pathology, Pfizer/Groton, CT; Member of Hepatotoxicity Working Group (HWG) of the PSTC (Predictive Safety Testing Consortium) (Con Position)

Robert Maronpot, DVM, MPH, DACVP, ABT- Maronpot Consulting LLC; 40+ years of toxicologic pathology experience, including Chief, Laboratory of Experimental Pathology, NIEHS/NTP

Moderated by RSESS VP - **Brian Short, DVM, PhD, DACVP**

Histopathology Evaluation for Biomarker Qualification-Background

- Pharmaceutical industry is developing novel biomarkers of of toxicity (CPath PSTC) and submitting info to FDA/EMEA
- FDA is facilitating the development of biomarkers by establishing clear and rigorous process for biomarker qualification
- Nephrotoxicity Working Group (NWG)
  - 2007: 30 rat toxicity studies completed to evaluate relationship between induced kidney pathology, traditional clinical chemistry parameters, and the performance of 7 new urinary markers of kidney injury
  - Pathology evaluation was nonblinded (Crissman et al, 2004)

Histopathology Evaluation for Biomarker Qualification-Background

- NWG Biomarker Qualification (2008)
  - Favorable qualification decision was announced by FDA and EMEA
  - FDA Biomarker Qualification Review Team (BQRT) expressed discomfort that the PSTC NWG pathologists followed a nonblinded approach instead of a blinded approach
  - Unintentional and observer bias could confound interpretation of biomarker qualification study outcome (Ransohoff, 2005)
- Hepatotoxicity Biomarker Working Group
  - 2010: Submission of Biomarker Qualification Package

Current Industry/Regulatory Interaction

- FDA is developing a guidance document on histopathology evaluation which will be issued for public comment
- FDA BQRT and Cpath PSTC agreed to request a joint review and seek decision from ACVP an STP as neutral 3rd parties to help resolve the issue
- STP is raising awareness and discussion of blinded/nonblinded histopathology pathology within the society and with other stakeholders (ACVP, SOT, global STPs)
- Related topics:
  - Biomarker Initiative: Clin Path evaluation may also need to be blinded
  - CBER/Gene Therapy perspective: In-life and postmortem assessments should be conducted in a blinded manner
  - Pathology peer review and definition of pathology raw data

Questions

- What are the advantages of blind evaluation?
- What are the disadvantages of blind evaluation?
- Nonblinded studies: Does anything need to be done to ensure a non-biased approach?