Respiratory Safety Pharmacology Endpoints in Toxicology

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Agenda

- Introduction
- Preliminary results from an Industry Survey
- Expert panel presentations
  - Pros: Jeff Tepper, PhD, DABT (Tepper Nonclinical Consulting)
  - Cons: Dennis Murphy, PhD, DABT (GlaxoSmithKline Pharmaceuticals)
- Open discussions
- Closing remarks
Introduction

- Inclusion of safety pharmacology in toxicology has received increasing attention over the last 2 years:
  - Scientific session at the 2010 Annual ACT Meeting in Baltimore
  - Continuing education session at the 2011 SPS meeting in Innsbruck, Austria
  - Industry survey launched by the SPS in August 2012
  - Discussed in a publication in the 2012 Safety Pharmacology Special Issue of the Journal of Pharmacological and Toxicological Methods (Ewart et al.)

- Upcoming scientific activities on SP in toxicology studies:
  - 2 additional webinars organized by the SPS in September 2012
  - One Continuing Education and one Plenary session at the 2012 Annual SPS meeting in Phoenix AZ
  - A scientific whitepaper from the SPS in 2013 integrating Industry survey results and Webinar discussions
Introduction: Methodologies

- Multiple monitoring methods are available for respiratory safety pharmacology in toxicology studies.
Preliminary Industry Survey Results

When thinking about safety pharmacology endpoints in toxicology studies, how would you describe your expertise?

Total of 361 participants

- 53.2% I am primarily a toxicologist
- 27.2% I am primarily a safety pharmacologist
- 19.6% I am equally a safety pharmacologist and toxicologist
Preliminary Industry Survey Results

In what sector is your organization?

- Pharmaceutical (primarily Novel Chemical Entities, NCEs)
- Biotech (primarily biological agents)
- Biopharmaceutical (mixture of both NCEs and biological agents)
- CRO
- Consultancy
- Technology provider
Have you had experience in designing, performing or interpreting the safety pharmacology component of a study when performed as part of a toxicology study?

- Yes: 67.2%
- No: 32.8%
On what study day(s) do you measure safety pharmacology endpoints in your toxicology study (day 1 = first day of dosing)? Choose all that apply.
Preliminary Industry Survey Results

Have you needed to stagger the study start in order to measure safety pharmacology endpoints on the appropriate day

- Never: 14.2%
- Occasionally: 26.1%
- Routinely: 59.6%
Preliminary Industry Survey Results

If you have conducted respiratory safety pharmacology investigations by adding endpoints to toxicology studies, which species have you used?

- Minipigs
- Mouse
- Rat
- Canine
- Nonhuman primate

Number of answers

Preliminary Industry Survey Results
Based on your opinion, S7A safety pharmacology endpoints in toxicology studies are generally appropriate for:

- Completely or partially agree = 61%

**Respiratory safety pharmacology for small molecules**
- Completely agree: 54
- Partially agree: 49
- Neither agree nor disagree: 33
- Partially disagree: 22
- Completely disagree: 11

**Respiratory safety pharmacology for large molecules**
- Completely agree: 54
- Partially agree: 48
- Neither agree nor disagree: 38
- Partially disagree: 13
- Completely disagree: 12
Preliminary Industry Survey Results

Have you submitted data to a regulatory agency where your S7 studies have been performed as part of a toxicology study rather than stand alone?

- Yes: 42.0%
- No: 58.0%
If you have received feedback from regulators, what did it indicate?

- 21 respondents indicated this methodology was considered acceptable by the agency.
- The agency suggested modification(s) to the design.
Increased sensitivity due to increased number of treated animals and assessment after repeat dosing

Overall reduction in number of animals used (3Rs)

Added value interpretation due to combined experimental endpoints in same animals

Practice acceptable to regulatory agencies

Cost savings on overall program development

Allows better risk mitigation by enabling more diverse evaluation panels for core battery systems

Based on your experience, which of the following do you consider a meaningful advantage of adding S7 safety pharmacology endpoints to regulatory toxicology studies:
Slides of expert panel members
Questions for open discussions

- Based on your opinion, S7A safety pharmacology endpoints in regulatory toxicology studies are generally appropriate for:
  - Respiratory safety pharmacology for small molecules?
  - Respiratory safety pharmacology for large molecules?
Questions for open discussions

- In your organization, has the ability to add safety pharmacology endpoints onto regulatory toxicology studies had any of the following consequences?
  - Allowed you to manage safety risk more effectively
  - Data contributed to the halting the progression of a compound
  - Data addressed a specific concern and supported the continuation of a compound
Questions for open discussions

- Based on your experience, please state any disadvantages of safety pharmacology investigations in toxicology studies?
  - Interferences on functional safety pharmacology endpoints by toxicology related activities in the room are unavoidable
  - Safety pharmacology investigations in toxicology studies could have significant interferences on toxicology endpoints and parameters.
  - Assignment of safety pharmacology expert technical staff to conduct investigations in toxicology studies is problematic
  - Sensitivity of safety pharmacology in toxicology is insufficient to provide an acceptable assessment in most programs
  - Safety pharmacology in toxicology represents a risk during regulatory submission as it is not an industry standard
Questions for open discussions

Based on your experience, please state any **advantages** of safety pharmacology investigations in toxicology studies?

- Increased sensitivity due to increased number of treated animals and assessment after repeat dosing
- Overall reduction in number of animals used (3Rs)
- Added value interpretation due to combined experimental endpoints in same animals
- Practice acceptable to regulatory agencies
- Cost savings on overall program development
- Allows better risk mitigation by enabling more diverse evaluation panels for core battery systems
Questions for open discussions

- Have you received regulatory feedback on inclusion of respiratory safety pharmacology in toxicology studies?
Thank you for your time and participation!

Looking forward to see you in Phoenix for the 2012 Annual SPS meeting