A Regulatory Perspective: Combined Safety Pharmacology and Toxicology Studies

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Disclaimer

The opinions expressed here are those of the speaker and do not necessarily reflect those of the FDA.
Focus of Presentation

- Does not repeat info from recent SPS webinars, “SP Endpoints in Tox Studies”
  - Webinars provided excellent discussions of strengths and weaknesses, relevant info from ICH guidances, etc.

- Limited to interviews with Pharm / Tox supervisors for 13 FDA/CDER drug review Divisions
  - Their individual Divisions’ experiences with combined Safety Pharm (SP) and tox studies
  - Their views of current advantages and disadvantages of combined SP and tox studies
  - Interviews completed prior to SPS webinars
Experience remains early, limited

- More CDER experience: combined studies in addition to stand-alone SP studies
  - Particularly ECGs during repeat dose tox studies

- Less CDER experience: combined studies instead of stand-alone SP studies
  - For many Divisions, rarely seen to date, except for biologicals and/or primate-only drugs
  - Opinions regarding combined studies instead of stand-alone SP studies are not yet fully formed
Range / rigor of data received

- CNS evaluations range from cageside observation only .. to full rodent FOB included in repeat-dose tox study

- CV evaluations range from single “snapshot” ECG on a restrained animal .. to repeated, 24-hour collection of multiple parameters

- Respiratory evaluations range from visual evaluation of rate and dyspnea .. to plethysmography
Combined studies requested?

- Combined studies are sometimes requested by Divisions where chronic effects have been a particular concern.
- Several Divisions routinely suggest combined studies for primate-only drugs.
- A few Divisions routinely suggest combined studies as an acceptable alternative to stand-alone SP studies.
Perceived advantages for CDER

- Only those advantages / disadvantages specifically mentioned by supervisors …
- Reduces animal use
- Can correlate safety pharm results with tox and toxicokinetic results from same study
- Some Divisions find that combined studies are more likely than stand-alone SP studies to include adequate high doses
- Includes both sexes
Perceived advantages for CDER

- Safety pharm parameters typically evaluated multiple times during repeat-dose tox studies
  - Potentially detect cumulative and/or chronic effects
  - Some adverse effects reduced following repeat doses
- Sample size (number of animals) may be larger, particularly for non-primate species
- Potentially useful where drug or metabolite accumulates with repeat doses
- Can potentially address reversibility
Perceived disadvantages for CDER

- Potentially reduced statistical power
  - Parallel groups design versus crossover study
  - Concern that variability in CV parameters among animals may be greater during tox studies than during stand-alone SP studies

- Greater confidence in stand-alone FOB
  - CNS evaluations during combined studies are often limited in scope
  - Are the personnel who perform behavioral observations during tox studies as well qualified as those who perform stand-alone CNS studies?
Perceived disadvantages for CDER

- Concern that tox study environment (noise, handling, procedures, etc.) may affect SP results
- Excessive heart rate (excitement?) may be more common during combined studies than during stand-alone SP studies?
  - Noted less often than a few years ago?
  - Can excitement also affect CNS evaluations in large animals during combined studies?
- Respiratory evaluations during combined studies are often limited to visual evaluation of rate and possible dyspnea
Other questions to P/T supervisors

- First SP evaluation on study day 1 or day 2?
  - Several = day 2, because handling for PK evaluations on day 1 will affect safety pharm parameters
  - A few = concern with day 2 due to rapid development of tolerance with some drugs
  - Some = insufficient experience for recommendation

- Concern if infection at implant site (catheter or telemetry system)?
  - Expected risk for drugs that affect immune function
Other questions to P/T supervisors

- Concern if increase in ventricular ectopic beats when left ventricular pressure catheter is used?
  - Expected risk, but limited experience

- CV parameters, preference for jacket or implanted telemetry system?
  - No preference
Other questions to P/T supervisors

- Is it OK to omit high-dose animals from SP evaluations where CNS or CV effects may occur due to toxicity?
  
  • Not recommended. Off-target CNS or CV effects can be dose limiting during clinical trials.
Suggestions from P/T supervisors

- If plan combined SP and tox studies instead of stand-alone SP, then consider including proposal in pre-IND discussions

- CNS methods validation
  - If evaluate CNS during combined studies instead of stand-alone CNS, then methods should be validated during simulated tox studies (same environment, handling, dosing, personnel, etc.)
  - Personnel and environment regarded as critical
  - Provide brief summary of validation
Suggestions from P/T supervisors

- Determine method sensitivity for CV SP
  - If evaluate CV parameters during combined studies instead of stand-alone CV, then method sensitivity should be tested during simulated tox studies (same environment, handling, dosing, personnel, etc.)
  - Provide brief summary of sensitivity validation

- Don’t reduce utility of SP evaluations by replacing stand-alone studies with “minimally acceptable” SP evaluations added to tox studies
Questions?