Target Animal Safety Evaluation in the Division of Therapeutic Drugs for Food Animals

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TAS technical section objectives

- Determine a margin of safety
  - For the intended dose, route, frequency, and duration of use in intended population
- Identify target organs and toxic effects, if possible
- Risk based inference of safety to the intended population

Innovation

- Early communication is essential for new ideas and alternative study designs
- Make good use of the Pharmacologic-Toxicologic characterization
Pharmacologic-Toxicologic Characterization

- Potential components
  - Pharmacokinetics, pharmacodynamics, and toxicology of the drug in target and non-target species
  - Literature or other publicly available information
  - Foreign adverse experiences
  - Pilot studies

Pharmacologic-Toxicologic Characterization

- Purpose
  - Identification of toxic syndrome and adverse effects
  - Justification for dose, duration, or frequency of treatment in study design
  - Assist in designing studies with focused evaluations
  - Justification for alternative, non-traditional approaches
  - Potentially eliminate the need for certain types of studies

Margin of Safety study design considerations

- Selection of dose and overdose levels
- Study duration
- Dose frequency
- Drug specific considerations
Selection of dose and overdose levels

- Common assumption when selecting dose and overdose level: If a drug has the potential to produce adverse drug reactions, this potential will be positively correlated with dose.
- 0, 1, 3, 5X is not always appropriate

Examples of Typical Dose-Effect Relationships

Paradoxical dose-effect relationships

CAUSE – competitive direct vs indirect effects

Drug +
Direct Effects +
Adverse drug reaction

Feedback system (possible threshold response)

Resulting Paradoxical Dose-Effect Relationships
Study Duration

- Common assumption when selecting study duration: If the drug has the potential to produce adverse drug reactions, this potential will be positively correlated with the duration of drug exposure.
- Appropriate study duration depends on the characteristics of the drug and its intended use
- Necropsies conducted at an appropriate time based on predicted toxic effects

Example: Nonlinear relationship between effect and duration of exposure

- Effect of 5-fluorouracil exposure duration on sperm count

Dose frequency

- Drugs intended for single dose administration
  - Consider both the active drug and metabolites when deciding the proper dose frequency and interval
- Extended release formulations: considerations include possible secondary peaks
- Drugs intended for repeated dosing
  - Generally use intended dosing interval
Other drug specific considerations

- Intra-mammary products
  - Udder irritation study
  - Systemic safety and reproductive safety evaluated if systemic absorption is a concern
- Topical products
  - Application site irritation
  - Consideration of the effect of licking
  - Ocular safety
- Nanotechnology
- Novel drug delivery platforms

Effect of licking in the TAS evaluation for topical products

- The way animals are housed in the study may affect the exposure (or blood levels).
  - housed to prevent social and self licking or housed to allow licking
- Which method of housing results in higher blood levels?
- Typically, the TAS study should be designed based on the worst case scenario for TAS, the situation that results in the higher blood levels

Additional laboratory safety studies (other than the margin of safety study)

- Reproductive safety
- Neonatal safety
- Injection site safety
- Specific animal class studies
Reproductive safety

- Dependent on the use of the drug - some indications preclude use in a particular sex or production stage
- Study examples
  - Male reproductive safety study
  - Female reproductive safety study
  - Evaluation of offspring
- Typically a 3X dose is compared to control (0X)

Male reproductive safety

- Evaluate continuous exposure through at least one spermatogenic cycle
- Examples of variables evaluated for cattle
  - Breeding soundness examinations
    - Conducted in accordance to the Society for Theriogenology guidelines
    - Semen collection pre- and post-treatment at a frequency to simulate daily sperm output (3 times/week)
  - Cow conception rate (if breeding study is conducted)

Female reproductive safety studies

- Estral cow safety
  - Evaluate effect of drug administered during the critical time points of the estrous cycle: folliculogenesis, ovulation, and post-ovulation
  - Examples of variables evaluated: conception rate, calving rate, abortion rate, calf normality (health, birth weight, 30 to 60 day body weights, and maturity/lack of congenital abnormalities at birth)
Female reproductive safety studies
Cattle examples

- Pregnant cow safety
  - Drug administered during each of the three trimesters of gestation
  - Examples of variables evaluated: calving rate, abortion rate, calf normality (health, birth weight, 30 to 60 day body weights, and maturity/lack of congenital abnormalities at birth)

Neonatal safety

- If target animal safety is demonstrated in neonatal animals, generally there will not be an age restriction listed on the label
- Neonatal animals may have special safety concerns
  - Examples
    - Differences in rumen function/maturity
    - Differences in intestinal absorption mechanisms
    - Differences in hepatic drug metabolism
    - Differences in rate of elimination

Injection Site Safety

- Stand alone study may not be required
- May be able to get injection site safety information from
  - Margin of safety study,
  - Effectiveness study,
  - Residue study, and/or
  - Pharmacokinetic study
Injection Site Study Design

- Dose: maximum volume
- Treatment groups
- Study duration
- Scoring/assessment of injection site safety
  - General behavior (e.g. lameness, retracting from touch, “tilting” in fish)
  - Skin appearance
  - Evidence of inflammation: swelling, heat, redness, hardness
  - Histopathology if unforeseen reactions or lesions

“Trim Loss” evaluation

- Trim loss concerns loss of edible tissue
  - Edible tissue = muscle tissue plus the overlying fascia, tissue not removed with the hide when standard hide removal procedures are utilized
- Labeling
  - A label precaution is the default
- Stand alone study not required
- Basis of study conclusions: trim loss precaution generally not necessary if the study shows an absence of gross lesions impacting edible tissue at a time point equal to or less than the minimum withdrawal time

“Trim loss” study design

- Dose
  - maximum volume
- Treatment groups
  - control group not required
- Study duration
  - Consider the withdrawal time
“Trim loss” study design

- Endpoints: gross necropsy/dissection of the injection site with photography
  - external surface,
  - subcutaneous tissue and underside of hide,
  - surface musculature and fascia, and
  - deep musculature
- Photographic considerations

Data submissions

- Organization of data
  - Create a clinical picture - correlate clinical signs, clinical pathology, and histopathology
- Data presentation
- Foreign data
  - units converted
  - all raw data included
  - appropriate documentation for personnel
  - certified translations

Labeling considerations
Challenges

- Reference ranges for clinical chemistry and hematology for some species or classes
- Differences between classes within species
- Aquaculture
  - Normal clinical chemistry and hematology values not available
  - Increased reliance on histopathology
  - Choosing a representative species

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