Mitigating Pain in Livestock: What Options are Available

NIAA 2014 Annual Conference
Omaha, Nebraska
April 2, 2014

Craig A. Lewis, DVM, MPH, DACVPM
Center for Veterinary Medicine
U.S. Food and Drug Administration,
Mitigating Pain in Livestock: What (Legal) Options are Available

NIAA 2014 Annual Conference
Omaha, Nebraska
April 2, 2014

Craig A. Lewis, DVM, MPH, DACVPM
Center for Veterinary Medicine
U.S. Food and Drug Administration,
Outline

• Background
• Drugs (approved, unapproved, compounded)
• Extralabel Drug Use
• Pain Mitigation from the Literature (Status)
• Questions
  – Under AMDUCA is extra-label use of analgesics and anesthetics permitted?
  – Is extra-label use of products restricted only to those products that have been approved by FDA and have an NADA or NDA number?
Pain Mitigation

• Disease pain
  – Cutaneous
  – Visceral – (serosa, distention, swelling)
  – Musculoskeletal – (bone, joint, muscle)
  – (Inflammatory)

• Surgical pain
  – General
  – Localized
Pain Mitigation (from the literature)

• NSAIDs
  – Aspirin
  – Sodium salicylate
  – Flunixin
  – Ketoprofen
  – Diclofenac
  – Phenylbutazone
  – Meloxicam
  – Carprofen
Pain Mitigation (from the literature)

• Local anesthetics
  – Lidocaine
  – Mepivacine
  – Bupivacaine
Pain Mitigation (from the literature)

- Barbiturates
  - Pentobarbital
  - Thiopental
- Acepromazine
- Benzodiasepines
  - Diazepam
  - Midazolam
- Azaperone
- Xylazine
Pain Mitigation (from the literature)

- Butorphanol
- Medetomidine
- Ketamine
- Tiletamine-zolazepam (Telazol)
- Guaifenesin
- Tramadol
- Yohimbine
Pain Mitigation (from the literature)

- Halothane
- Isoflurane
- Propofol
- Guaifenesin
- Tramadol
Approved Animal Drugs

• To be legally marketed, an animal drug must be the subject of
  – an approved new animal drug application (NADA)
  – an approved generic application [abbreviated new animal drug] application] (ANADA)
  – a conditional approval
  – an index listing
Approved Human Drugs

• To be legally marketed, a human drug must be the subject of
  – an approved new drug application (NDA)
  – an approved generic application [abbreviated new drug application] (ANDA)
  – An OTC Drug Monograph
Unapproved Animal Drugs

• No pre-approval review

• No post-approval monitoring

• May unfairly compete against approved products

• Reduces the availability of legal, reviewed, tested and monitored drug products
Unapproved Animal Drugs

- Animal drugs illegally marketed in the United States that have not been approved by the Food and Drug Administration (FDA)

- Unapproved animal drugs have not been reviewed under FDA's legal review processes
Compounded Animal Drugs

• If compounded from approved drugs (as starting ingredients) **MAY** be legal under ELU regulations

• If compounded from bulk ingredients **IS** considered an unapproved animal drug

• Zero tolerance for compounding from bulk ingredients for food-producing animals
Compounded Animal Drugs

- Unknown quality control/manufacturing standards
- Unknown assurance of purity, potency, or stability
- Potential animal safety and efficacy issues
- Potential for unknown or unsafe residues
- Difficult to monitor – No reporting requirements (even less than for other unapproved animal drugs)
Extralabel Drug Use

• Extralabel is the use of an approved drug in a manner that is not in accordance with the approved label directions.
  – e.g. indication, species, dosage level, frequency, route of administration

• Allows veterinarians to prescribe extralabel uses of certain approved animal drugs and approved human drugs
Extralabel Drug Use

“Such use is limited to treatment modalities when the health of an animal is threatened or suffering or death may result from failure to treat.”
Extralabel Drug Use

- **Must** be by or on the order of a veterinarian within the context of a “valid veterinarian-client-patient relationship”
- **Must** not result in violative residues
- **Must** be in conformance with all other parts of extralabel drug use regulation (21 CFR Part 530)
- **Must** not use drugs prohibited from extralabel use
Extralabel Drug Use

“Establish a substantially extended withdrawal period prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information.”
Extralabel Drug Use

“Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment.”
Extralabel Drug Use

- Approved animal drugs
- Approved human drugs
- Conditionally approved animal drugs
- Indexed animal drugs
- Medicated feeds
- VFD drugs (veterinary feed directive)
- Human OTC monographed drugs
- Unapproved animal drugs
- Drugs compounded from approved drugs
- Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
  - Approved human drugs
  - Conditionally approved animal drugs
  - Indexed animal drugs
  - Medicated feeds
  - VFD drugs (veterinary feed directive)
  - Human OTC monographed drugs
  - Unapproved animal drugs
  - Drugs compounded from approved drugs
  - Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
- Approved human drugs
  - Conditionally approved animal drugs
  - Indexed animal drugs
  - Medicated feeds
  - VFD drugs (veterinary feed directive)
  - Human OTC monographed drugs
  - Unapproved animal drugs
  - Drugs compounded from approved drugs
  - Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
- Approved human drugs
- Conditionally approved animal drugs
  - Indexed animal drugs
  - Medicated feeds
  - VFD drugs (veterinary feed directive)
- Human OTC monographed drugs
- Unapproved animal drugs
- Drugs compounded from approved drugs
- Drugs compounded from bulk ingredients
Extralabel Drug Use

✓ Approved animal drugs (Rx or OTC)
✓ Approved human drugs
× Conditionally approved animal drugs
× Indexed animal drugs
  • Medicated feeds
  • VFD drugs (veterinary feed directive)
  • Human OTC monographed drugs
  • Unapproved animal drugs
  • Drugs compounded from approved drugs
  • Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
- Approved human drugs
- Conditionally approved animal drugs
- Indexed animal drugs
- Medicated feeds
  - VFD drugs (veterinary feed directive)
  - Human OTC monographed drugs
  - Unapproved animal drugs
  - Drugs compounded from approved drugs
  - Drugs compounded from bulk ingredients
Extralabel Drug Use

✓ Approved animal drugs (Rx or OTC)
✓ Approved human drugs
× Conditionally approved animal drugs
× Indexed animal drugs
× Medicated feeds
× VFD drugs (veterinary feed directive)
  • Human OTC monographed drugs
  • Unapproved animal drugs
  • Drugs compounded from approved drugs
  • Drugs compounded from bulk ingredients
Extralabel Drug Use

✓ Approved animal drugs (Rx or OTC)
✓ Approved human drugs
✗ Conditionally approved animal drugs
✗ Indexed animal drugs
✗ Medicated feeds
✗ VFD drugs (veterinary feed directive)
✗ Human OTC monographed drugs
• Unapproved animal drugs
• Drugs compounded from approved drugs
• Drugs compounded from bulk ingredients
Extralabel Drug Use

✓ Approved animal drugs (Rx or OTC)
✓ Approved human drugs
✗ Conditionally approved animal drugs
✗ Indexed animal drugs
✗ Medicated feeds
✗ VFD drugs (veterinary feed directive)
✗ Human OTC monographed drugs
✗ Unapproved animal drugs
  • Drugs compounded from approved drugs
  • Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
- Approved human drugs
- Conditionally approved animal drugs
- Indexed animal drugs
- Medicated feeds
- VFD drugs (veterinary feed directive)
- Human OTC monographed drugs
- Unapproved animal drugs
- Drugs compounded from approved drugs
  - Drugs compounded from bulk ingredients
Extralabel Drug Use

- Approved animal drugs (Rx or OTC)
- Approved human drugs
- Conditionally approved animal drugs
- Indexed animal drugs
- Medicated feeds
- VFD drugs (veterinary feed directive)
- Human OTC monographed drugs
- Unapproved animal drugs
- Drugs compounded from approved drugs
Pain Mitigation
(from the literature)

• NSAIDs
  – Aspirin
  – Sodium salicylate
  – Flunixin
  – Ketoprofen
  – Diclofenac
  – Phenylbutazone
  – Meloxicam
  – Carprofen
Pain Mitigation (from the literature)

- NSAIDs
  - Aspirin
    - Unapproved animal – cattle, swine, sheep, poultry (marketed)
    - OTC monograph – human (marketed)
  - Sodium salicylate
  - Flunixin
  - Ketoprofen
  - Diclofenac
  - Phenylbutazone
  - Meloxicam
  - Carprofen
Pain Mitigation (from the literature)

• NSAIDs
  – Aspirin
  – Sodium salicylate
    • Unapproved animal – cattle, swine, poultry (marketed)
  – Flunixin
  – Ketoprofen
  – Diclofenac
  – Phenylbutazone
  – Meloxicam
  – Carprofen
Pain Mitigation (from the literature)

• **NSAIDs**
  – Aspirin
  – Sodium salicylate
  – **Flunixin**
    • Approved animal – horses, cattle, swine (marketed)
  – Ketoprofen
  – Diclofenac
  – Phenylbutazone
  – Meloxicam
  – Carprofen
Pain Mitigation (from the literature)

- **NSAIDs**
  - Aspirin
  - Sodium salicylate
  - Flunixin
  - Ketoprofen
    - Approved animal – horses (marketed)
  - Diclofenac
  - Phenylbutazone
  - Meloxicam
  - Carprofen
Pain Mitigation (from the literature)

- **NSAIDs**
  - Aspirin
  - Sodium salicylate
  - Flunixin
  - Ketoprofen
  - Diclofenac
  - **Phenylbutazone**
    - Approved animal – horses (marketed)
  - Meloxicam
  - Carprofen
Pain Mitigation
(from the literature)

• Local anesthetics
  – Lidocaine
  – Mepivacine
  – Bupivacaine
Pain Mitigation (from the literature)

- Local anesthetics
  - Lidocaine
    - Unapproved animal, injectable – cattle (marketed)
    - Unapproved animal, topical (marketed)
  - Mepivacine
  - Bupivacaine
Pain Mitigation
(from the literature)

• Barbiturates
  – Pentobarbital
  – Thiopental
• Acepromazine
• Benzodiazepines
  – Diazepam
  – Midazolam
• Azaperone
• Xylazine
Pain Mitigation
(from the literature)

• Barbiturates
  – Pentobarbital
  – Thiopental
    • Approved animal – dog, cats (not marketed)
• Acepromazine
• Benzodiazepines
  – Diazepam
  – Midazolam
• Azaperone
• Xylazine
Pain Mitigation
(from the literature)

• Barbiturates
  – Pentobarbital
  – Thiopental
• Acepromazine
• Benzodiazepines
  – Diazepam
    • Approved animal – dogs (not marketed)
  – Midazolam
• Azaperone
• Xylazine
Pain Mitigation (from the literature)

- Barbiturates
  - Pentobarbital
  - Thiopental
- Acepromazine
- Benzodiazepines
  - Diazepam
  - Midazolam
    - No approved/marketed animal products
- Azaperone
- Xylazine
Pain Mitigation (from the literature)

- **Barbiturates**
  - Pentobarbital
  - Thiopental

- **Acepromazine**

- **Benzodiazepines**
  - Diazepam
  - Midazolam

- **Azaperone**
  - Approved animal – swine (not marketed)

- **Xylazine**
Pain Mitigation (from the literature)

- Barbiturates
  - Pentobarbital
  - Thiopental
- Acepromazine
- Benzodiazepines
  - Diazepam
  - Midazolam
- Azaperone
- Xylazine
  - Approved animal drug – cats, dogs, horses, deer (marketed)
Pain Mitigation
(from the literature)

- Butorphanol
- Medetomidine
- Ketamine
- Tiletamine-zolazepam (Telazol)
- Guaifenesin
- Tramadol
- Yohimbine
Pain Mitigation
(from the literature)

- **Butorphanol**
  - Approved animal – dogs, cats, horses (marketed)
- **Medetomidine**
- **Ketamine**
- **Tiletamine-zolazepam (Telazol)**
- **Guaifenesin**
- **Tramadol**
- **Yohimbine**
Pain Mitigation (from the literature)

- Butorphanol
- **Medetomidine**
  - Approved animal – dogs, cats (marketed)
- **Ketamine**
- Tiletamine-zolazepam (Telazol)
- Guaifenesin
- Tramadol
- Yohimbine
Pain Mitigation
(from the literature)

- Butorphanol
- Medetomidine
- **Ketamine**
  - Approved animal – cats, primates (marketed)
- Tiletamine-zolazepam (Telazol)
- Guaifenesin
- Tramadol
- Yohimbine
Pain Mitigation
(from the literature)

• Halothane
• Isoflurane
• Propofol
• Guaifenesin
• Tramadol
Pain Mitigation
(from the literature)

- Halothane
- **Isoflurane**
  - Approved animal – dogs, horses (marketed)
- Propofol
- Guaifenesin
- Tramadol
Under AMDUCA is extra-label use of analgesics and anesthetics permitted?
Under AMDUCA is extra-label use of analgesics and anesthetics permitted? 

Yes
Is extra-label use of products restricted only to those products that have been approved by FDA and have an NADA or NDA number?
Is extra-label use of products restricted only to those products that have been approved by FDA and have an NADA or NDA number?

Yes
Is extra-label use of products restricted only to those products that have been approved by FDA and have an NADA or NDA number?

Yes

(for the most part)