Environmental Safety Assessment of New Animal Drugs

Wesley Hunter, Ph.D.
U.S. Food and Drug Administration
Center for Veterinary Medicine
Environmental Safety Team

Outline

- Legal mandates and implementation
- Overview of the CVM NEPA process
- Categorical exclusions
- Environmental Assessments
- Points to consider

Federal Food, Drug and Cosmetic Act

Target Animal Safety
Target Animal Effectiveness
Human Food Safety
Manufacturing
Other Public Health
National Environmental Policy Act (NEPA, 1969)

- Basic national charter for the protection of the environment
- NEPA requires Federal Agencies consider the environment
- FDA Regulation: 21 CFR 25.15(a)
  - All applications or petitions requesting agency action require the submission of an Environmental Assessment (EA) or a claim of categorical exclusion (CE).

FDA Role - Actions

- Examples of agency actions that require environmental review:
  - Allow investigations under INAD
  - Approval of NADA, ANADA, FAP, supplements
- Environmental review focuses on:
  - Use
  - Excretion
  - Disposal
  (not usually manufacturing)

Council on Environmental Quality (CEQ)
Implement NEPA
http://www.whitehouse.gov/ceq/

CFR, Title 40, Part 1500 - 1508

Categorical Exclusions
- from the need to prepare an EA or EIS

Environmental Assessments (EA)
- Public document; determines whether to prepare a finding of no significant impact (FONSI) or an EIS

Environmental Impact Statements (EIS)
- Public document detailing the environmental impacts of actions, including Record of Decision (ROD)
Overview of CVM NEPA Process

Proposed Action
(new drug, indication, etc.)

Meets criteria

Categorical Exclusion

Categorical Exclusions

- actions which the agency has predetermined do not individually or cumulatively have a significant effect on the human environment; and therefore, ordinarily do not require the preparation of an EA or EIS

- Generally based on limited use and/or supplements to approved drugs that do not increase the use

Categorical Exclusions for Animal Drugs

21 CFR 25.33
- (a) (1) – (7) use does not increase;
- (b) Reserved
- (c) Naturally occurring
- (d) (1) – (5) nonfood, anesthetic, nonsystemic topical and ophthalmic, minor species, prescription for terrestrial animals
- (e) INAD
- (f) no longer relevant
- (g) Withdrawal NADA or ANADA
- (h) Withdrawal FAP
Extraordinary Circumstances

21 CFR 25.21 – FDA Regulations
21 CFR 1508.27 – NEPA Examples

- FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the proposed action may significantly affect the quality of the human environment.

Extraordinary Circumstances

21 CFR 25.21 – FDA Regulations

- At the expected level of exposure there is the potential for serious harm to the environment.
- Actions that adversely affect a species or the critical habitat of an endangered or threatened species.

Claiming a Categorical Exclusion

21 CFR 25.15(d)

Applicant:
- states that the action requested qualifies for a categorical exclusion
- cites the particular categorical exclusion that is claimed (only cite the most relevant if several apply)
- verifies by statement that to the applicant’s knowledge (given a reasonable search for information) no extraordinary circumstances exist

The Agency:
- agrees that the action qualifies and that no extraordinary circumstances exist
Overview of CVM NEPA Process

Environmental Assessments

- Environmental Assessments
  - 21 CFR 25.40(a), ...an EA is a concise public document that serves to provide sufficient evidence and analysis for an agency to determine whether to prepare an Environmental Impact Statement (EIS) or a Finding of No Significant Impact (FONSI)
  - FDA is ultimately responsible for the scope and content of each EA (although they are usually prepared by the drug sponsor)

Preparing an Environmental Assessment Document

- Concise, objective, balanced document
- Focus on relevant environmental issues relating to the use of the drug and its disposal
- Provide sufficient evidence and analysis to determine the need for a FONSI or EIS
- Description of potential risk mitigations
Format of an EA

- Generally follows a risk assessment process
  - Hazard identification
  - Exposure characterization
  - Effects characterization
  - Risk characterization
  - Consequence assessment
  - Mitigations/management
  - appropriate for public display and allow the public to understand the agency's decision (21 CFR 25.40(a))
- Guidance for Industry 61 gives general guidance on the content and format of an EA

Overview of CVM NEPA Process

Environmental Assessment (EA)

- Proposed Action (new drug, indication, etc.)
- Categorical Exclusion
- Extraordinary circumstances
- Acceptable risk
- Finding of No Significant Impact (FONSI)
- Environmental Impact Statement (EIS) & Record of Decision (ROD)
- Unacceptable risk
- Risk Mitigation Options

Environmental Assessment
Harmonized Guidance

- Phase I (March 7, 2001)
- Phase II (January 9, 2006)
- These guidances have been developed by an international group (VICH) to harmonize the data requirements for approval of veterinary drug products in the U.S., European Union, Australia and Japan.
Overview of CVM NEPA Process

- Proposed Action (e.g., new drug or use)
- Meets criteria
- Categorical Exclusion
- Extraordinary circumstances
- Finding of No Significant Impact (FONSI)
- Environmental Impact Statement (EIS) & Record of Decision (ROD)
- Environmental Assessment (EA)
- Unacceptable risk
- Risk Mitigation Options

Phase I analysis – (Exposure)
Phase II analysis - Tier A (Acute)
Phase II analysis - Tier B (Chronic/reproductive)
Phase II analysis - Tier C (Further analysis)

Finding of No Significant Impact (FONSI)

Environmental Impact Statement (EIS) & Record of Decision (ROD)

Overview of CVM NEPA Process

- Phase I analysis – (Exposure)
  - Does not meet criteria
  - Unacceptable risk
  - Extraordinary circumstances
  - Environmental Assessment (EA)
  - Finding of No Significant Impact (FONSI)
  - Environmental Impact Statement (EIS) & Record of Decision (ROD)

Veterinary Scenarios

- Intensively reared animals
- Pasture animals
- Aquaculture
Phase I Guidance
- A limited exposure assessment
  - Uses a pre-determined environmental concentration
- Recommended Predicted Environmental Concentration (PEC) values
  - ≥100 ppb in soil
  - ≥1 ppb in water
  - Phase II analysis

Phase II Guidance
- Focus on ecosystem protection
- Laboratory studies on properties, environmental fate, and effects on invertebrates, fish, plants
- Measurement endpoints: mortality, immobilization, reproduction, growth
- Biogeochemical cycling (nitrogen and carbon transformation)

Phase II Risk-Quotient Method

Exposure Assessment
- Environmental release
- Fate/Distribution
- Predicted Environmental Concentration (PEC)

Effects Assessment
- Proposed Use
- Single species toxicity data
- Extrapolation (AF)
- Predicted No Effect Concentration (PNEC)

Risk Characterization
- RQ = PEC/PNEC
- ≥1 → move to next tier
Exposure Assessment

Use pattern

Chemical & environmental fate properties
(metabolism, excretion, storage time, degradation in storage, adsorption, etc.)

Manure loading rate, water use and management

PEC

Exposure Assessment

Duration Frequency Seasonal Distribution

Chemical Use

Number of Animals Treated Administration (e.g., feed, injection, bath)

Species & Diseases

Effects Assessment

- Laboratory tests (single species; standardized tests)
- Acute tests in Tier A *Terrestrial as well*
- Chronic tests in Tier B

*Model Aquatic Ecosystem*
TIER A Studies

Physical-chemical Studies
- Water Solubility
- pH
- Melting Temperature
- Vapour Pressure
- Octanol/Water Partition Coefficient

Environmental Fate Studies
- Soil adsorption/desorption
- Degradation in soil
- Degradation in aquatic systems
- Photolysis (optional)
- Hydrolysis (optional)

Aquatic Effects Studies
- Algae growth inhibition
- Daphnia acute immobilization
- Fish acute toxicity
  Includes testing of saltwater species if relevant for drug use

Terrestrial Effects Studies
- Terrestrial plant growth
- Microorganisms (N transformation)
- Earthworm subacute/reprod.
- Dung fly and beetle larvae (for certain ectoparasiticide)

TIER B Studies

Environmental Fate Study
- Bioconcentration in fish

Aquatic Effects Studies
- Daphnia or crustacean reproduction
- Fish, early-life stage
- Sediment invertebrate toxicity
  Includes testing of saltwater species if relevant to drug use/disposal pattern

Terrestrial Effects Studies
- Earthworm chronic
- Terrestrial plants growth – 2 additional species + sensitive spp. from Tier A
- Nitrogen fixation - extension of Tier A study for an additional 100 days

Risk Characterization

- Risk screening based on a risk quotient (RQ)

\[ \text{RQ} = \frac{\text{PEC}}{\text{PNEC}} \]

- PNEC = Effects endpoint ÷ Assessment Factor (AF)
  - Lab to field extrapolation
  - Interspecies and intraspecies differences in sensitivity
  - Acute to chronic extrapolation

Predicted Environmental Concentration (PEC)
Risk Characterization
Predicted No Effect Concentration (PNEC)
### PNECs for TIER A

**Surface water**
- Endpoint | AF
- algae (96 h) | EC50 | 100
- invertebrate (48 h) | EC50 | 1000
- fish (96 h) | LC50 | 1000

**Soil**
- Endpoint | AF
- earthworm (chronic) | NOEC | 10
- higher plants (3 species) | EC50 | 100
- microorganisms (28 days) | < 25% of control

**Dung (pasture animals)**
- Endpoint | AF
- dung fly | EC50 | 100
- dung beetle | EC50 | 100

### PNECs for TIER B

**Surface water**
- Endpoint | AF
- algae (96 h) | NOEC | 10
- invertebrate (21 d) | NOEC | 10
- fish (28 d) | NOEC | 10
- sediment species (varies) | NOEC | 10

**Soil**
- Endpoint | AF
- earthworm | no recommendation
- higher plants (more species) | NOEC | 10
- microorganisms (100 days) | < 25% of control

**Bioaccumulation**
- BCF > 1000 l/kg ⇒ investigate secondary poisoning

### Tier C – Further Analysis

- Specialized Laboratory and/or Field Testing
  - Pulsed exposure studies
  - Microcosm and mesocosm studies
  - In-stream studies
  - Test additional species

- Refined Risk Analysis
  - Species sensitivity distribution analysis
  - Probabilistic exposure analyses
  - Specialized environmental fate modeling

- Risk Mitigation and Management (Labeling)
  - Use and/or disposal restrictions
  - Mandatory treatment requirements
  - Water quality benchmarks for use in NPDES
Study Design

- Adequate and well-controlled studies
- Follow FDA and/or OECD GLP standards
- OECD guidelines are generally accepted and recommended
- Methods should be adequately validated

Use of peer-reviewed journal articles to support key data

- Acceptable approach for some endpoints
- Studies must be adequate and well-controlled
- Well documented and corroborated
- See Guidance for Industry 106 for more information

Overview of CVM NEPA Process
Environmental Assessment Document

- Following approval, the EA is put on public display:
  http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm

Points to Consider

CE submissions

Applicant should:

- Ensure that the submission includes the correct and complete CFR citation

- If no extraordinary circumstances exist, ensure that submission includes a statement certifying that to the sponsor's knowledge, no extraordinary circumstances exist

- Ensure that the submission includes basic information about the drug (e.g., dose, dosage form, species, indications for use, etc.)
Points to Consider
EA submissions

Applicant should:

- Ensure that the public EA does not contain any proprietary information
- Ensure that studies referred to in the EA are summarized in the EA
- Ensure that important scientific statements contain reference citations
- Ensure that metabolites and/or degradates are adequately considered

Communication

- We encourage communication early and often.
- If you have an alternative approach or unique situation that differs from our current guidance, please let us know. We are open to considering other approaches.

Thank You

Wesley Hunter, Ph.D.
FDA/CVM
Environmental Safety Team, HFV-162
7500 Standish Place
Rockville, MD 20855
240-276-9548
wesley.hunter@fda.hhs.gov