

SPECIAL SESSION
ADVANCING AQUACULTURE DRUG APPROVALS BY
STRATEGIC COORDINATED RESEARCH

1ST MEETING OF THE
NATIONAL AQUACULTURE DRUG RESEARCH FORUM
August 05, 2004

Held in conjunction with the 10th Annual Drug Approval Coordination Workshop

MISSION STATEMENT

“To advance scientific knowledge and coordinate research activities
to expedite the approval of new animal drugs.”

The goal of the forum is to develop a strategic plan component to work on issues relative to drug approval research activities, including (1) providing a forum for the exchange of information and mutual education between CVM review teams and representatives from academia, the pharmaceutical industry, aquaculture industry, and other government agencies, and (2) to create a mechanism to broadly disseminate information relative to drug approval research activities.

ANALYTICAL METHODS VALIDATION ISSUES

Leader: Jeff Meinertz

Current Members: Kevin Greenlees (initial CVM contact),
Paul Duquette, Larry Schmidt, and Art Craigmill (?)

This project team will work on the validation of analytical methods used in various stages of the new animal drug approval process.

Objectives for the sub-group include:

1. Identify the types of methods. These include research methods, dose-verification methods for feed or other administration vehicles, for water, and for the aquatic environment.
2. Identify and collate existing guidance documents.
3. Identify, as appropriate, others involved in analytical methods development, including CVM, USGS, the pharmaceutical industry, and others.
4. Engage in discussions to assure mutual understanding of the validation requirements and to identify gaps, if any.
5. Determine appropriate means to share the validation information with the aquaculture drug development community.

ANTIMICROBIAL RESISTANCE ISSUES IN AQUACULTURE

Leader: Vacant

Current Members: Kevin Greenlees (initial CVM contact), Christine Moffitt,
Paul Duquette, Rosalie Schnick, and Tom Bell

The team will collate, and or develop, aquatic microbiology information necessary for a microbial safety risk assessment.

Two specific microbiological issues identified are:

1. Identification of the relevant micro-organisms, including normal flora, pathogens, and zoonotics, in key aquatic species.
2. Discussion of potential interaction between the life-stage of the aquatic target animal and the makeup of the endogenous microflora.

TARGET ANIMAL SAFETY / EFFICACY

Leaders: Jim Bowker and Don Prater (initial CVM contact)

Current Members: Mark Gaikowski, Jeff Rach, Pat Gaunt, Dave Straus, Renate Reimschuessel, Anita Kelly, Dan Carty, and Molly Bowman

This team will work to resolve issues associated with conducting lab and field efficacy trials and target animal safety studies to support drug approvals in a broad array of fish species.

1. Pilot Studies
 1. Determine most sensitive life-stage
 2. Determine doses (range)
 3. Determine temperature (range) resulting in highest mortality/pathology
 4. Target tissues to be sampled
 5. Tolerance (10x standard dose for specified duration)
 6. Margin of safety (1x, 3x, 5x standard dose for 3x the standard duration)
 7. Dose-titration vs. Dose-confirmation - difference between
 8. Predictive models
2. Label Claim
 1. Single vs. multiple exposures
 2. Use pattern (control of mortality vs control of disease (wt change)
 3. Define doses
 4. Match dose range for all technical sections
3. Dose-verification
 1. Sampling strategy (bath / feed)
 2. Data analysis/reporting
 3. Analytical methods (do they exist ? Problems encountered with analytical labs (Limit of quantification, limit of detection, quality assurance, use of controls and reporting their values)
 4. Acceptable target ranges (bath / feed)
 5. Sample storage (bath / feed)
 6. Contaminated feed - acceptable levels of non-target antibiotic in feed, use of sensitivity tests to prove target pathogens are sensitive to target antibiotic and resistant to non-target antibiotic
4. Anesthesia
 1. Experimental design
 2. Define endpoints
 3. Define margin of safety
 4. Predictive models

TARGET ANIMAL SAFETY / EFFICACY (CONTINUED)

5. Crop Grouping
 1. Phylogenetic
 2. Temperature
 3. Fresh vs. Marine species
 4. Compound
 5. Issues that need to be considered: economic importance of the species of fish, maintenance of fish in the laboratory, importance of a therapeutant in a particular species of fish, adverse reactions of a therapeutant in a particular species (may require additional species for testing)

6. Secondary Variables
 1. Water quality
 2. Standard criteria for feeding behavior observations (ordinal scale)
 3. Standard criteria for general behavior observations
 4. Uneaten feed

7. Pathologies
 1. Tissues to be examined - short list vs long list (finfish, crustaceans, mollusks)
 2. Tissue sampling techniques for histology
 3. Histologist/pathologist reports - report vs histologists notes

8. Randomization
 1. Fish-to-tanks
 2. Condition-to-tanks
 3. Experimental units
 4. Life-cycle stage
 5. Sampling fish for histology

9. Model Trials
 1. Routes of infection and Infection models- immersion, injection (identify disease models from literature, presentations, etc) - in the wild, many bacterial infections are believed to be transmitted in the water or by co-habitation with infected fish. In laboratory settings, for many species of fish or for many bacteria, this method does not achieve a high enough infection rate.
 2. Stressors (used to concurrently exasperate infectious diseases such as crowding; hypoxia, abrasion, etc are believed to duplicate conditions causing infections of fish in the wild. Comments or clarification of acceptable methods of stressing fish in the wild and in the literature would be helpful.
 3. Selection of pathogens
 4. Levels of mortality (similar to natural disease levels)
 5. Disease verification
 6. Timing of when medicated feed should be administered post-challenge. Times reported in the literature range from a few hours to a few days after inoculation.

TARGET ANIMAL SAFETY / EFFICACY (CONTINUED)

10. Clinical Field Trials
 1. Dealing with concurrent infections
 2. Dealing with re-infection
 3. Post-treatment period
 4. Enumeration of fishes (accounting for missing fish at termination through mathematical formulas, observation, experience?)
 5. Cumulative mortality
 6. Disease verification - sampling for fish health evaluations
11. Animal Welfare
 1. Methods of euthanasia
 2. >50% mortality not needed
12. Trials to evaluate the efficacy of external Parasiticides
 1. Defining reasonable primary response variable
13. Flow-thru vs. Static Bath
14. Study Protocols and Final Study Reports (to expedite CVM review)
 1. Standard approaches to development
 2. Standard format to assemble documents
 3. Standard format to provide CVM with summarized data and statistical output
 4. Standard approach to characterize feeding behavior and general fish behavior
 5. Elements that must be included in Study Protocols or suggestion regarding how to measure elements and present to CVM
 6. Provide GCP and GLP guidance to facilities including copies of protocols to use as templates, SOP, source for personnel training, etc.

Priorities (in no particular order):

Pilot studies required to determine treatment/exposure regimens, life stages, water temperature to test, short and long list of histo tissues that can be evaluated (instead of only long list) and testing logistics - how best to submit to CVM for concurrence

Model trials

Crop grouping or identifying representative cool and warmwater fish that will satisfy completing technical sections for efficacy and TAS

Sharing approaches used to measure/evaluate secondary response variables - then establishing "standard" approaches; providing GCP and GLP guidance

ENVIRONMENTAL RISK ASSESSMENT

Leaders: Chuck Eirkson

Current Members: Carla Fromm (EPA), Gary Jensen (USDA), Eric Silberhorn (FDA), Mark Gaikowski (USGS), Tom Bell (USFWS), Rod Williams (Arizona), Jerre Mohler (USFWS)

This team will work to address the challenges associated with assessing the relative environmental risks of animal drugs used in aquaculture to support the new animal drug approval process.

The current objectives of the group are:

1. Identify additional members for the group to provide input for various aquaculture management systems and other critical stakeholders.
2. Collect data from available sources (e.g., literature, research reports, thesis, etc.) that are necessary for an aquaculture environmental assessment (EA) for an NADA for specific drugs used in aquaculture. This objective will include:
 - a. Developing a key words list for searching existing sources for information (i.e., information listed in the VICH Phase II Guidance for aquatic exposures http://vich.eudra.org/pdf/10_2004/GL38_st7.pdf).
 - b. Develop a list of drugs that are considered priority for obtaining information for the environmental assessment.
 - c. Collect and collate the available information.
 - d. Identify existing data gaps for future research.
3. Develop standard methods for calculating a predicted environmental concentration (PEC) for use in environmental risk assessment for aquaculture drug products. This includes:
 - a. Agreeing on the appropriate management systems that need PEC (e.g., flow-through, ponds, net pens, intensive culture, etc.).
 - b. Collecting information on flow rate and facility dilution mechanism to provide for development of standard calculations for critical management systems.
 - c. Working with EPA and state offices to identify and, if possible, incorporate allowable surface water dilutions (e.g., mixing zones) for use in standard methods for calculating PECs.
 - d. Develop standard methods for calculating PECs.