9TH MEETING OF THE NATIONAL AQUACULTURE DRUG RESEARCH FORUM

FRIDAY JUNE 12, 2009
8:00 – 10:15 AM

Location:
La Quinta Inn & Suites Downtown Conference Center
Little Rock, Arkansas
Room Bush 41

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 drug/chemical industry, aquaculture industry, and other government agencies, (2) establishing a repository of useful information and documents, and (3) to create a mechanism to broadly disseminate information relative to drug approval research activities.

<u>Forum Co-Chairs:</u>

USDA-ARS – SNARC	Dr. Dave Straus
USDOI-USFWS - AADAP	Jim Bowker
USDOI-USGS – UMESC	Mark Gaikowski
USFDA-CVM - OR	Dr. Renate Reimschuessel

Agenda:

1. Brief summary of 8th Meeting of the NADRF meeting minutes
2. Discuss issues/challenges relative to conducting field trials to evaluate the effectiveness of chemotherapeutants to control ectoparasite infestation in finfish. The goal of this session will be to resolve as many of the issues listed below (and any others that may come up) or form a Working Group Committee and ask for volunteers to resolve the issue through development of the appropriate products (e.g., identify and cite appropriate literature, develop white paper arguments, etc.)

   Based on results from the "parasite' survey, ectoparasites of primary concern include (in order of importance):
   - Protozoans of primary concern are 1) *Ichthyobodo* (costia), 2) *Trichodina,* and 3) *Chilodonella*
   - Monogeneans of primary concern are 1) *Gyrodactylus,* and 2) *Dactylogyrus*
   - Crustaceans of primary concern are 1) *Argulus*, and 2) *Salmonicola*

Focus on how resolution of the topics below fit into hypothesis testing, designing and conducting the study, analyzing data, and interpreting study results:

1. Describe similarities and differences between Regulatory and Academic Science – click here to view attached Supplemental Document #1
2. Terms commonly used to describe parasite population (e.g., prevalence, incidence, density, intensity, abundance, etc.) – click here to view attached Supplemental Document #2
3. Label claim – control mortality vs control parasites
4. Treatment efficacy – statistical difference between treated and control and achieving a treatment success threshold; posttreatment period
    i. For example: Significant difference in the number of parasites on treated fish than on control fish plus >75% reduction in the number of parasites on treated fish
5. Experimental unit – tank, fish, or fish within a tank (nested); sample size
    i. For example: can a 75% reduction in parasite numbers be detected with 95% confidence when n = 3?
6. Parasite identification – to genus or genus/species – is it possible?
7. Populations comprised of a single genus vs. communities
8. Distribution of parasite on host
9. Lumping similar parasites based on general characteristics (e.g., sessile ciliates) and development of white paper(s); dealing with the potential number of field trials to demonstrate treatment efficacy against the primary protozoan and monogenean parasites – can other parasites be lumped with one or more of the primary protozoan and monogenean parasites (e.g., *Trichodina ssp.*, *Epistylis ssp.*, and *Trichophyra ssp.*)
10. Enumeration - Quantitative vs semi-quantitative; dealing with Too Numerous to Count; counting live parasites from (1) wet-mounts, (2) preserved samples, or (3) histology slides; assigning semi-quantitative categories (e.g., mild, moderate, severe) and associated # parasites/each category
11. Sampling fish, sub-sampling areas on fish, sub-subsampling areas of a prepared microscope slide
12. Sampling schemes
    i. Sampling live fish periodically during the study
    ii. Sample with or w/o replacement
    iii. Maintaining similar fish densities in test tanks – effect of fish density on parasite infestation
    iv. Dealing with fish mortality during the study – utility of parasite enumeration data from dead fish
13. Concomitant fish pathogens (e.g., bacteria, fungus)
14. Secondary variables – resolution of clinical signs

Considerations

Number of field effectiveness trials required to demonstrate that a parasiticide effectively controls infestations of *Ichthyobodo* (costia), *Trichodina*, *Chilodonella*, *Gyrodactylus*, and *Dactylogyrus* in all freshwater finfish and the cost of conducting the studies:

5 ectoparasites
6 fish species (2 representative coldwater, 2 representative coolwater, and 2 representative warmwater finfish)
Total number of studies = 30 studies

Approximate cost of conducting the required studies
30 studies
$30,000/study
Total approximate cost = $900,000

Is it worth it?

Supplemental Document #1

Science Policy Intro
Regulatory vs. Academic Science

Center for Science and Technology Policy Research

Regulatory vs. Academic Science

The standards of academic science are inappropriate to the needs and constraints of regulatory science. Both try to understand and explain complex, multivariate, non-linear nature, but they have vastly different constraints. Thus asking a panel of academic scientists to apply the standards applied in writing for journals and applying for research grants to making regulatory decisions is inherently unfair.

Academic and Regulatory Science *are* different:

	Regulatory Science	Academic Science
Institutions	Government/industry	Universities
Goals	• Information needed to meet regulatory requirements and to provide reliable information for decision makers. • Research questions are framed by legislators and regulators and often have social and economic implications. • Ultimate goal is conflict resolution via public debate over competing interests and values.	• Original research framed by scientists and driven by rational analysis and expert judgment. • To expand understanding and knowledge of the natural world through an ongoing process of questioning, hypothesizing, validation, and refutation.
Role of Uncertainty	Predictive certainty is required by the political process and by legal requirements.	Uncertainty is expected and "embraced."
Products	"Gray literature," baseline data, monitoring data, regulatory documents	Published papers, presentations at professional meetings.
Time-frame	Determined and driven by statute,	Open-ended

	regulation, and the political process; finite and often quite short (90 days to 2-4 years)	
Political Influence	Directly influenced by politics: upper-level administrators are appointed by the President; funding is at the will of Congress; ultimate oversight is by the courts.	Indirectly influenced by the researcher's own political philosophy and by their perception of the preferences of grant and tenure review committees.
Accountability	Legislatures, courts (moderated to some degree by Daubert v. Merrill Dow, deference, and to some extent, the precautionary principle), and the public	Professional peers
Incentives	Compliance with legal requirements	Professional recognition, advancement in tenure system; university administration

Supplemental Document #2

General Terms to describe parasite populations (see Bush et al. 1997. Parasitology meets ecology on its own terms: Margolis et al. revisited. Journal of Parasitology 83(4):575-583).

Click here for graphic examples to supplement the definitions.

Quantitative descriptors of parasite populations (point estimates based on samples from the while population of hosts).

When infected and non-infected fish in a population are evaluated

Prevalence – the number of hosts infected with ≥ 1 individuals of a particular parasite divided by the number of hosts examined (alternative terms – percent infected).

One of the most common—and least misused—terms used in parasitology.

Abundance – is the number of individuals of a particular parasite in/on a single host regardless of whether or not the host is infected. Abundance is a form of density, and it differs from intensity in that an intensity of 0 is not possible, whereas an abundance of 0 is appropriate.

Mean abundance – the total number of individuals of a particular parasite species in a sample of a particular host species divided by the total number of hosts of that species examined (including both infected and non-infected hosts). It is thus the average abundance of a parasite species among all members of a particular host population

Only infected fish in a population are evaluated

When you can count every parasite on the sampling unit (i.e., fish):

Intensity – the number of individuals of a particular parasite in a single infected host. Intensity is a form of density with the sampling unit specifically defined as an individual infected host.

Mean intensity – is the average intensity of a particular species of parasite among the infected members of a particular population of host species. In other words, it is the total number of parasites of a particular species found in a sample divided by the number of hosts infected with that parasite.

When you cannot count every parasite on the sampling unit:

Density – number of individuals of a particular parasite in a measured sampling unit taken from a host in units of area (or volume or weight). Not appropriate when the denominator is "host." When using "host" as the denominator, the terms intensity and abundance are more concise and preferable. Density can be measured quantitatively or semi-quantitatively (as follows):

Quantitative density: Exact number of parasites per sampling unit (area, volume, or weight).

Semi-quantitative density: Score (rank) number of parasites as, e.g., “light,” “moderate,” or “heavy” per sampling unit (area, volume, or weight). For example: “Light” could be < 5 parasites per unit area; “moderate” could be 5 – 10 parasites per unit area; and “heavy” could be > 10 parasites per unit area.

Used when starting with a healthy population

Incidence – the number of new hosts that become infected with a particular parasite during a specified time interval divided by the number of uninfected hosts present at the start of the time interval (alternative terms – attack rate or colonization rate).

This is a term used to describe the risk of acquiring new infections by individuals in a population of hosts. Term most commonly used to monitor the spread of clinical disease in populations.

Quantitative Descriptors

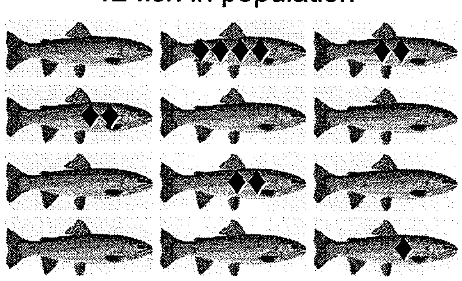
Bush et al. 1997. Parasitology meets ecology on its own terms. Journal of Parasitology 83(4):575–583.

A common vocabulary facilitates effective communication

Prevalence

- Percent of population infected with ≥ 1 individuals of a given parasite

12 fish in population



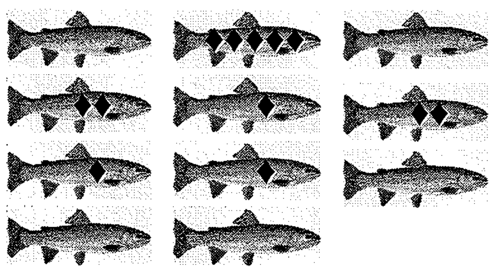
5 fish infected with ≥ 1 parasite

Prevalence
(5 / 12) × 100 = 42%

Mean (±SD) Abundance

- Mean (±SD) abundance of a given parasite among all members of a fish population.

10 fish in population



12 parasites

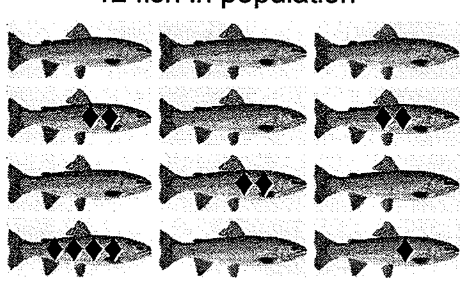
Mean (±SD) abundance
Mean = (12 / 10) = 1.2
SD = 1.5

Intensity

Applies only to infected fish, and when you can count each parasite.
Fish is sampling unit.

- Number of parasites of a particular species in a single infected host

12 fish in population



5 fish infected

Intensity
1 + 2 + 2 + 2 + 4 = 11 parasites
Mean = (11 / 5) = 2.2
Range = 1 to 4

Density: an estimate of parasite burden

Applies only to infected fish, and when you cannot count each parasite.

Fish is sampling unit, and you must subsample.

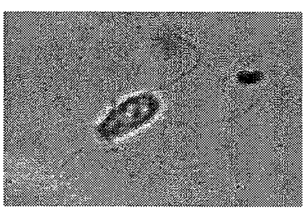
- Number of individuals of a particular parasite in a measured sampling unit taken from a host or habitat. Expressed in units of area, volume , or weight, e.g.,

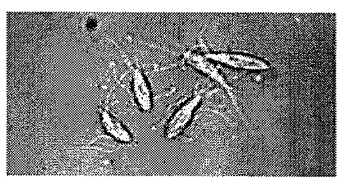
  - **Quantitative**: Exact number of parasites per sampling unit (area, volume, weight)

  - **Semi-quantitative**: Score (rank) number of parasites as light, moderate, or heavy per sampling unit (area, volume, weight)

Density

Semi-quantitative example





Score = 1	Score = 2	Score = 3
light	moderate	heavy
< 5 parasites per unit area	5 – 10 parasites per unit area	10 parasites per unit area

Incidence

Number of new hosts that become infected with a particular parasite during a specified time interval. Applies only to uninfected individuals, without regard to number of individuals with existing infections. Useful for estimating risk of acquiring a new infection, and also can be used to monitor spread of disease.

Example: N = 100 susceptible individuals (none infected)

Day 1	Day 2	Day 3
100 susceptible 7 get infected	93 susceptible 15 get infected	78 susceptible 10 get infected
Daily attack rate: (7 / 100) = 0.07	Daily attack rate: (15 / 93) = 0.16	Daily attack rate: (10 / 78) = 0.13