U.S. Fish & Wildlife Service

The Aquatic Animal Drug Approval Partnership Program

"Working with our partners to conserve, protect and enhance the Nation's fishery resources by coordinating activities to obtain U.S. Food and Drug Administration approval for drugs, chemicals and therapeutants needed in aquaculture"

AADAP Aquatic Animal Drug Approval Partnership Program

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WHAT'S SHAKIN'

The 17th Annual USFWS Aquaculture Drug Approval Coordination Workshop is almost here: This year the Workshop will once again be held in Bozeman, Montana USA, and this year the Workshop, *per se*, is taking place from August 2nd through the 4th. Two other related professional activities are being planned to be held in conjunction with this year's Workshop. The American Fisheries Society - Fish Culture Section's Working Group on Aquaculture Drugs, Chemicals and Biologics will be held during the Workshop (planned for Wednesday morning, 3 August 2011). For more information on this meeting, click here for a general agenda, and/or contact Jesse Trushenski (email: saluski@siu.edu) or Jim Bowker (email: jim_bowker@fws.gov).

Additionally, an *ad hoc* meeting entitled "Discussion Session with CVM to Develop Strategies to Resolve Drug Approval and Post Approval Issues" (aka "the listening session") is scheduled to be held on Monday, 1 August 2011. This meeting will be held at the nearby U.S. Fish & Wildlife Service's Bozeman Fish Technology Center from 8:00 am to 4:00 pm. For more information on this meeting, contact Jesse Trushenski (email: saluski@siu.edu) or Jim Bowker (email: jim_bowker@fws.gov) and/or refer to the Working Group on Aquaculture Drugs, Chemicals, and Biologics' update section on page 2 of the Newsletter.

As is always the case when the Workshop is held in Bozeman, the Sweet Pea Festival activities are scheduled for the same week and the following weekend. And, for you veterans of the Workshop in Bozeman, you may be interested in knowing that the Welcome Social on Monday (1 August) will be held where it has usually been held in the past. Hope to see you'all here in Bozeman!

Check the AADAP website for more details, and be sure to register on-line at http://tinyurl.com/3v2tyok.

Approved Aquaculture Drugs - Quick Desk Reference Guide - "SOLD OUT:" The long-awaited AADAP - AFWA - AFS's Quick *Desk Reference Guide To: Approved Drugs for Use in Aquaculture* was made available on Tuesday, 24 May 2011. Unfortunately, in little over a week we were completely "sold out;" by Tuesday 31 May 2011 all 1,000 copies had been spoken-for via our on-line request page. There is still hope for those that did not get their requests in quick enough - as we speak we are in the process of obtaining a second printing. Please check the AADAP website for availability information. For those unaware of what it is, the "*Desk Reference*" comprises all the information contained in the "*Approved Drugs for Use in Aquaculture*" poster, as well as examples of "...how to calculate..." the proper dose or concentration of approved drugs as per label instructions. The "*Desk Reference*" can be ordered (free of charge, when it is available) or downloaded via AADAP's website at: http://www.fws.gov/fisheries/aadap/desk-reference_introduction.htm.

Progress update from the American Fisheries Society - Fish Culture Section's (AFS-FCS)

Working Group on Aquaculture Drugs, Chemicals, and Biologics (WGADCB): Since meeting in New Orleans earlier this year, the WGADCB leadership has been working hard to organize a "listening session" or stakeholders' meeting with key representatives of FDA CVM to discuss strategies to improve the approval process for drug approvals. The meeting is scheduled for Monday, August 1, 2011 from 8 am - 4 pm at the USFWS Bozeman Fish Technology Centers' Piper Building. Please note that the WGADCB meeting is scheduled just before the 17th Annual USFWS Aquaculture Drug Approval Coordination Workshop, also taking place in Bozeman the 1st week of August—one-stop shopping for aquaculture drug info!

Originally planned as an AFS congressional briefing, it was decided during an early planning meeting that a listening session would be a more productive approach to addressing challenges to getting new drugs approved for use in fish culture. Over the past few months, a series of talking points were developed to articulate these challenges, ranging from data requirements to establish efficacy and safety for aquaculture drugs to complexities associated with labeling and packaging restrictions. After being refined and distributed to WGADCB participants for comment, the talking points were distributed to the relevant groups within CVM to identify issues that could be readily addressed during the first listening session. Although an extensive list of issues was compiled from input by many stakeholders, it was mutually decided that the first meeting will focus on issues that can be readily addressed by the CVM staffers in attendance. To this end, a travel request has been submitted by CVM staff to their management requesting travel funds for a relatively large contingent of CVM staff (including a meeting facilitator) to attend and participate. CVM staff and WGADCB Co-chairs will narrow the list of Talking Points to an agenda of items which can be addressed directly and hopefully resolved during the 1st meeting. Unresolved issues will not be left by the wayside, but rather slated for subsequent meetings. Staff at CVM are encouraging broad participation to this meeting so that as large a group as possible hears information directly from the source. In you are interested in attending the listening session, please contact WGADCB Co-Chair Jesse Trushenski (saluski@siu.edu) or Jim Bowker (email: jim_bowker@fws.gov) and make your travel plans accordingly. Those interested in attending the session will be provided with the agenda as soon as it is available. The agenda will also be posted on AADAP's website.

Activities and projects like the listening session are drawing attention and plenty of positive feedback from various allied organizations, including the U.S. Aquaculture Society (USAS) and the Fish Health Section (FHS) of the American Fisheries Society. To encourage broader participation in the WGADCB, USAS Board Member Andy Lazur has been appointed as a WGADCB Co-Chair. This is an important step toward recognizing the common interests of the USAS in aquaculture drug approvals and use. Welcome Andy—we look forward to your participation! The FHS has also expressed interest in having a seat at the Co-Chairs table, and we look forward to bringing them into the fold as partners in the WGADCB. As more and more individuals and entities become involved in the WGADCB, it is likely that some administrative arrangements will have to change to grow with the group and allow us to stay nimble and responsive to emerging aquaculture drug issues. Nonetheless, we think this is a very positive development and look forward to working with our partners, new and old, in supporting the development, approval, availability, and judicious use of drugs, chemicals and biologics for use in aquaculture.

For more information on current WGADCB activities, please see the meeting minutes (click here), contact one of the co-chairs, or better yet, come to our next meeting! The next meeting of the WGADCB will be held in conjunction with the 17th Annual USFWS Aquaculture Drug Approval Coordination Workshop in Bozeman, Montana at 10:30 AM, Wednesday 3 August 2011. Stay tuned to the AADAP website for WGADCB meeting scheduling announcements.

Text provided by Jesse Trushenski; Fisheries and Illinois Aquaculture Center; Southern Illinois University Carbondale; Carbondale, Illinois USA.

Ray Brunson receives S.F. Snieszko Distinguished Service Award: At the recent combined Western Fish Disease Workshop and annual meeting of the American Fisheries Society - Fish Health Section, Ray Brunson (recently retired Director of the U.S. Fish & Wildlife Service's Olympia Fish Health Center) received the Fish Health Section's most prestigious award, the S.F. Snieszko Distinguished Service Award. Ray received the award, as did Drew Mitchell from the U.S. Department of Agriculture's Stuttgart National Aquaculture Research Center; Stuttgart, Arkansas USA (see USDA's Corner, page 10 of this Newsletter for more regarding Drew).

Ray Brunson on the right; photo courtesy of Dr. Mike Mauel, Mississippi State University.

In the words of Dr. James Winton (U.S. Geological Survey's Western Fisheries Research Center; Seattle, Washington USA), "...Ray's contributions include [those from the] areas of: virology, bacteriology, parasitology, immunology, toxicology, physiology, nutrition and environmental health...he may be best known for his important work on viral hemorrhagic septicemia (VHS)… Ray's life-long commitment to research, teaching and service in the field of fish health embodies all the attributes of Stan Snieszko in whose honor the award is presented."

Congratulations Ray, ya' done us proud !!

AADAP DRUG UPDATES

General: Summer has finally arrived and with it comes the season when the AADAP research team transitions from writing Final Study Reports to getting busy conducting pivotal field efficacy trials. It's also the time of year when we begin to hear back from CVM regarding our submissions from the previous year. Although we've been in this game long enough to think we know how CVM will view our submissions, you never really know until you get the response letter in the mail. To see the latest on what's going on and how we fared last year, read on.

AQUAFLOR® (florfenicol) Update:

Just one more BKD efficacy study!!: Well, just when we thought we were pretty much done with conducting AQUAFOR®/BKD/Chinook salmon field efficacy trials, we got word that we will have to conduct one more study.

In the last newsletter, we stated that two studies were conducted in collaboration with Doug Munson (Idaho Department of Fish and Game) to evaluate the efficacy of AQUAFLOR® at a dosage of 15 mg florfenicol per kg fish body weight per d for 10 d to control mortality caused by bacterial kidney disease (BKD; causative agent, *Renibacterium salmoninarum*) in Chinook salmon. Results showed that (1) at the end of the 14-d posttreatment period, mean cumulative mortality in treated tanks was significantly lower than that in control tanks, (2) dose verification results were within acceptable limits imposed by CVM, and (3) a sufficient number of moribund fish were sampled from each tank during the study for fish health. To our delight, the studies were accepted by CVM as demonstrating evidence of effectiveness. However, the effectiveness technical section for AQUAFOR®/BKD/Chinook salmon remains incomplete because both studies were conducted at the same location by the same investigator using fish from similar reference populations.

To complete the technical section, another study will have to be conducted, preferably at a different facility by a different investigator. Based on our experience, such a request will likely prove problematic….any volunteers? We thank Doug Munson for his commitment to conduct these studies and coming in on weekends for most of the summer to collect the necessary data. Fear not Doug, we'll do what we can to find another study site so your efforts will not be wasted.

Channel Catfish Pituitary Update:

Environmental Assessment status: In the last newsletter, we mentioned that we were developing an Environmental Assessment (EA) for the use of channel catfish pituitary (CP) as a spawning aid in a variety of warmwater finfish species. On 28 April 2011, we submitted the EA to CVM requesting a formal review of the document and that CVM consider the EA for CP complete. We're in their queue and the clock is ticking; we hope to hear back from CVM by the end of October that our request has been granted.

Status of other technical sections: In anticipation that the EA will ultimately be accepted by CVM, we are working with the sponsor to schedule a product development meeting with CVM to find out what will be required to complete the effectiveness, safety, and product chemistry technical sections. We've had some preliminary discussions with Dr. Chris Green (Assistant Professor of Aquaculture, Louisiana State University, Aquaculture Research Station) to identify the metric to be used to establish effectiveness, and how many adequate and well-controlled trials should be required to complete the effectiveness and safety technical sections. We're optimistic that completing these technical sections won't be too problematic. However, we are very concerned whether it is at all possible to complete the Product Chemistry (PC) requirements for a crude product like CP. From our perspective, the sponsor will only be successful gaining FDA approval if CVM's Division of Manufacturing Technologies Biotherapeutics Team allows some provisions to satisfy their requirements for a product that is extracted from a fish, dried, reconstituted with saline solution, and injected into other fish. Obviously, CP is not your typical pharmaceutical company-type drug product. Let's hope that CVM sees it that way too.

AQUI-S®20E and Benzoak® update:

Pivotal effectiveness studies: We're ready to launch into a field season full of sedative effectiveness trials. We had been waiting to launch until we got a chance to look at some data being generated by researchers at the USGS Upper Midwest Environmental Sciences Center (UMESC; La Crosse, Wisconsin USA). The UMESC lab's study compared a simple analytical technique (UV-Vis spectrophotometry) to an HPLC procedure for the determination of eugenol (active ingredient in AQUI-S®20E) concentrations in water.

Recently, we received information from UMESC indicating that the UV-Vis spectrophotometric method: (1) compared favorably with the HPLC method, (2) was specific for eugenol under a wide range of environmental conditions, and (3) that eugenol degraded to vanillin very, very slowly. We felt that this information was sufficient for us to not wait to formally hear from CVM that the UV-Vis method is acceptable to verify concentrations of eugenol in effectiveness and safety trials, and that we would begin evaluating the effectiveness of AQUI-S®20E immediately.

We have also been working with the sponsor for Benzoak® (active ingredient benzocaine) to verify that their UV-Vis spectrophotometric method is indeed specific for benzocaine and is also likely to be accepted by CVM. In both cases it's a risky decision on our part to launch studies for CVM might not accept either method and thereby not accept results from any efficacy studies we conduct using a spectrophotometric method. Our thinking is "hey, what's a little risk when you're already living on the edge."

In spite of the fact that we've just recently begun, we're done testing rainbow trout, will complete testing cutthroat trout by mid-July, and have already generated "supportive" data on walleye, hybrid striped bass, largemouth bass, and Arctic char. We have also identified several facilities (i.e., USGS Upper Midwest Environmental Sciences Center, La Crosse, Wisconsin USA; Southern Illinois University, Carbondale, Illinois USA; Florida Bass Conservation Center, Webster, Florida USA; Genoa National Fish Hatchery, Genoa, Wisconsin USA) that have access to a variety of cool- and warmwater finfish, and are coordinating with lead researchers at these facilities to arrange for us to "take our show on the road" and generate all the data necessary to complete the "all freshwater finfish" effectiveness technical sections for both sedatives.

SLICE® (emamectin benzoate) Update:

Ectoparasite efficacy studies: As reported in the last issue of the newsletter, AADAP submitted final study reports to CVM for each of the three efficacy studies we conducted in 2010 to evaluate the effectiveness of SLICE® administered in feed as an ectoparasiticide. In all three studies, emamectin benzoate was administered at a dosage of 50 µg per kg fish body weight per d for 7 d to reduce infestations of *Salmincola californiensis* in rainbow trout. The first two studies had a 30 d posttreatment period, and the third study a 42 d posttreatment period. Although the 90% reduction threshold in infestation level (required by CVM to demonstrate efficacy) in treated tanks compared to control tanks was achieved in only the third study, a significant difference ($P < 0.001$) was detected in the mean abundance of parasites between treated and control tanks at the end of the posttreatment period in all 3 studies. Although we have not received official word yet from CVM, rumor has it that in order to complete the effectiveness technical section for rainbow trout we may need to conduct/submit an additional study (or two) that demonstrates a 90% reduction in parasite infestation level at the end of the posttreatment period. In May 2011, we initiated a field efficacy study at the Maramec Spring Hatchery (Missouri Department of Conservation, St. James, Missouri USA) working with manager Wesley Swee and his staff. *Salmincola* spp. infestation on rainbow trout has been a persistent problem at the Maramec facility. Fortunately, Wes and crew were willing/able to allocate fish and redirect their time to conducting an efficacy trial. More recently, we have been back in touch with Scott LaPatra at Clear Springs Foods' Snake River Research Facility in Buhl, Idaho. Two of the previously submitted efficacy studies noted above were conducted at Clear Springs Foods, and Scott has graciously once again volunteered his time and staff to assist in conducting yet another study that will start sometime within the next few weeks. The study in Missouri and the Idaho studies are/will be conducted with a 42 d posttreatment period. Thanks much to Wes and Scott for stepping up!

TERRAMYCIN® 200 FOR FISH Update:

Systemic columnaris medicated feed efficacy study: In April 2010, our effectiveness research protocol for TERRAMYCIN® 200 FOR FISH (TM200) to control mortality caused by susceptible pathogens in a variety of freshwater finfish was accepted by CVM. At the time, plans were in place to conduct a study in cooperation with Mike Matthews at the Florida Bass Conservation Center. The study, using channel catfish, was scheduled to commence as soon as the fish broke with disease. Unfortunately, and as is so often the case with aquatic animal efficacy studies, when you want the fish to get sick they don't, and hence, the study never left the ground. We've been in touch with Mike early this year and he is anticipating sick fish this summer. He has set aside a population of largemouth bass and as soon as the fish break with systemic columnaris, he'll launch the first TM200 study. Let's keep our fingers crossed, and maybe if we hope that they stay healthy, they will break with columnaris. We'll keep you informed.

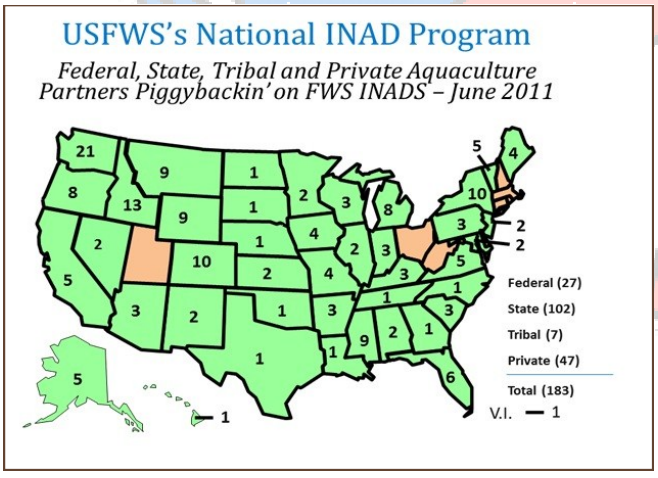
FINS & TAILS, BITS & BOBBERS

Calendar Year 2010 NIP Study Submission Statistics: Last year was a very busy year for conducting INAD studies, and with your help, we were able to collect a wealth of very useful/real world data. Here are some of the summary statistics from 2010 studies:

1) Number of completed study reports submitted to the AADAP Office – 694 reports
2) Number of reporting facilities - 149
3) Number of INADs used - 17
4) Number of treated fish – 124.1 million fish
5) Species of fish treated – 18 salmonid species; 39 non-salmonid species; 8 marine species; and 1 shellfish species
6) Percentage of studies that appeared efficacious/or efficacy data not needed due to the efficacy section being complete = 90%
7) Number of Quarterly Reports submitted to FDA/CVM – 61 reports
8) Number of Annual Reports to be submitted to FDA/CVM – 17 reports

Thank you to everyone for your hard work in contributing data to the AADAP Office, and please be aware that this data is being used to support new and/or expanded drug labels.

National INAD Program (NIP) Update: The NIP continues to be an extremely successful program for the USFWS and partner facilities/agencies. To date in 2011 there are 183 federal, state, private, and tribal facilities participating in 43 different states and one U.S. territory. Currently 16 different INADs are available for use.



EDITORIAL

Getting More Biological Value from Aquaculture Drug Efficacy and Target Animal Safety Trials

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Editor's note: The views expressed by Mr. Carty are not necessarily those of the U.S. Fish & Wildlife Service (USFWS) nor the USFWS Aquatic Animal Drug Approval Partnership Program.

Introduction and Objectives

Demonstrating efficacy and target animal safety are among the many challenges associated with obtaining U.S. Food and Drug Administration (FDA) approvals for new or expanded uses of therapeutic drugs and other chemicals in aquaculture (Greenlees 1997; Story 2005). In this article, I describe the current FDA-driven approach to efficacy and target animal safety testing, highlight limitations of that approach, and suggest ways to increase the biological inferential value of efficacy and target animal safety trials. I conclude that increasing the biological inferential value of individual trials coupled with periodic reviews of all efficacy and target animal safety data "on file" at FDA could not only prove to be a more efficient route to obtaining approvals of new or expanded uses of therapeutic drugs and other chemicals in U.S. aquaculture but also prove to be more relevant to postapproval uses by end-users in production settings.

Current Approach to Efficacy and Target Animal Safety Testing

The current approach to efficacy and target animal safety testing is driven by FDA's interpretation of the ambiguous data requirements delineated in Title 21 of the U.S. Code of Federal Regulations. Most efficacy and target animal safety testing is conducted under study protocols written by sponsors or researchers and submitted to FDA for critical review. When the required protocol revisions have been completed and FDA "concurs" with a protocol, it means only that the agency "fundamentally agrees" with the stated hypothesis, experimental design and procedures, data analysis methods, and planned interpretation of observed results. A series of individual efficacy and target animal safety trials is then conducted, and — in most cases — trial results are submitted to FDA in individual final study reports. Also —I n most cases — FDA accepts or rejects each final study report on its own merit. The FDA considers the efficacy and target animal safety technical sections "complete" when the required number of trials has been accepted.

The current approach to designing and conducting efficacy and target animal safety trials is largely based on null hypothesis significance testing (Nakagawa and Cuthill 2007), i.e., that there is *no statistically significant difference* in a primary response variable between treatment groups (efficacy) or among exposure groups (target animal safety). Primary response variables include endpoints such as percent mortality, percentage of fish sedated to handleable, percentage of fish with fluorescent-marked vertebrae, percentage of fish with a particular gross or histological lesion, or average number of ectoparasites per fish. In an efficacy trial, the

preferred outcome is to observe a statistically significant difference (reject the null hypothesis) between treated and nontreated (control) groups and use that information to document that treatment "worked." In a target animal safety trial, the preferred outcome is to *not* observe a significant difference (not reject the null hypothesis) among exposure groups and use that information to document that a proposed treatment regimen is safe to target animals even when the animals are exposed at up to five times a proposed treatment dose for up to three times a proposed treatment duration. Rejecting or not rejecting a null hypothesis is usually done by comparing an appropriate statistical test's *P*-value (range, ~0 to 1) with a specified statistical significance level (e.g., 0.1, 0.05; Kain 2005). Roughly translated, a *P*-value is the probability of obtaining a result at least as large as that observed in a trial when, in fact, there is no difference between treatment groups or among exposure groups (Glantz 2002). In general, null hypotheses are rejected when *P*-values are "small" and not rejected when *P*-values are "large." The FDA usually requires *P*-values to be less than 0.05 to reject null hypotheses in efficacy trials but only less than 0.1 to reject null hypotheses in target animal safety trials. Inherently, it is statistically "harder" to demonstrate efficacy and "easier" to detect target animal safety problems.

In addition to null-hypothesis significance testing, the current approach to efficacy testing sometimes includes a biological "threshold" requirement. For example, in a skeletal marking trial conducted with oxytetracycline-treated feed, we not only had to demonstrate that the percentage of marked fish in the treated group was significantly greater than that in the control group but also that at least 70% of the treated group was marked. In a trial testing hydrogen peroxide for the control of the ectoparasite *Gyrodactylus salmonis* in rainbow trout and in trials testing emamectin benzoate-medicated feed for the control of the ectoparasite *Salmincola californiensis* in rainbow trout, we not only had to demonstrate that mean abundance of the ectoparasite in question differed significantly between treated and control groups but also that percent reduction in mean abundance (treated group compared with control group) was at least 90% (based on an FDA/CVM guideline used in efficacy trials for the control of parasites in terrestrial animals). Setting and achieving biological thresholds can increase the inferential value of efficacy trials; however, those thresholds must be realistic and reflect end-user expectations. Particularly in the case of emamectin benzoate for use to control *Salmincola californiensis*, it is too early to tell if a 90% reduction in mean abundance is achievable and of biological importance in all situations, let alone a realistic target.

Limitations of the Current Approach

Efficacy trials in which there are treated and control groups can be designed to answer three basic questions (underlying concept as described by Kain 2005): (1) could the observed outcome have occurred solely by chance (statistical significance), (2) how large was the observed difference between the treated and control groups with respect to the primary response variable (biological effect size), and (3) was the observed difference meaningful to the affected individual or population (clinical or biological importance). Null hypothesis significance testing via *P*-values can answer the first question but cannot answer the second and third questions and does not allow a reasonable confidence interval (range of likely outcomes) to be placed around observed results (Nakagawa and Cuthill 2007).

Null hypothesis significance testing is even more problematic in target animal safety trials when — as preferred — no significant differences are found among exposure groups. Although it seems counterintuitive, it has been noted that the only inference that can be made from a nonsignificant result is that a test was inconclusive (Fisher 1935; Glantz 2002; Nakagawa and Cuthill 2007). However, a finding of no significant difference in a target animal safety study is often interpreted as evidence of "no adverse effect or effects" (underlying concept as described by Nakagawa and Cuthill 2007). In other words, it is human nature to assume that if nothing went wrong during a trial, then not only was everything all right during the trial but that everything will be all right in future trials (Hanley and Lippman-Hand 1983). Of course, this assumption can be incorrect simply because of small sample size, natural variation, or both.

Finally, the usual practice of submitting individual final study reports to FDA and having each report reviewed on its own merit precludes extracting biological information that could be obtained by analyzing groups of related trials as a whole.

Increasing Biological Inferential Value

Increasing the biological inferential value of aquaculture drug efficacy and target animal safety trials will require changing the current approach to these trials. First, sponsors, researchers, and regulators will need to agree *a priori* (up front) on the types and magnitudes of differences between treated and control groups (efficacy trials) or among exposure groups (target animal safety trials) that will be considered "biologically important." Then, experimental designs will need to be developed that have enough statistical power to have a reasonable chance of detecting those differences when they occur and that allow reasonable confidence limits to be placed around observed results. Placing reasonable confidence intervals around observed efficacy results would give end-users a "better idea" of what to expect from treatment and make it easier for end-users to judge when treatment is beneficial. Moreover, even in target animal safety trials in which no mortality, no gross

lesions, and no histological lesions are observed, the maximum risk (upper confidence limit) of adverse effects occurring in the future can be estimated by a variety of mathematical or statistical approaches (Rumke 1975; Hanley and Lipman-Hand 1983; Jovanovic and Levy 1997; Ludbrook and Lew 2009). Estimating the risk of adverse events occurring in the future would make it easier for end-users to understand and take steps to minimize risks associated with treatment—especially those risks associated with potential inadvertent overdosing, overexposing, or both.

Up-front estimates of types and magnitudes of biologically important effects could be derived from pilot work, peer-reviewed and gray literature, expert opinion, Investigational New Animal Drug exemption data, or — as a start — multisite- and meta-analyses of the efficacy and target animal safety data on file at FDA. A multisite analysis can help evaluate efficacy and target animal safety across several geographic locations but is limited to trials conducted with a single fish species, single fish pathogen, and single drug. On a broader scale, a meta-analysis combines the results of many similar trials to identify overall trends in observed results (e.g., means and confidence intervals) and identify variables (e.g., fish species, life stage, sex, and stage of maturity; geographic location; water quality; timeliness of treatment; or drug dose, duration, and frequency) that have had the greatest influence on results observed to date (underlying concept as described by Nakagawa and Cuthill 2007). Future efficacy and target animal safety trials could then maximize data collection for "more important" variables and minimize data collection for "less important" variables. Hence, periodic multisite- and meta-analyses of the data on file at FDA could help refine or redirect the focus of future efficacy and target animal safety testing.

Conclusion

Some who read this article might disagree outright with the suggestions presented, and undoubtedly there are short-comings to some of those suggestions. However, the goal of this editorial is to contribute in a positive way to the ongoing discussion about how to make the aquaculture drug-approval process more efficient and relevant to end-users. Biology might not be the driving factor behind this discussion; however, I believe that placing less emphasis on null hypothesis significance testing *per se* while placing more emphasis on the biological benefits and risks associated with treatment could lead to reducing the number of trials required to obtain FDA approvals of new or expanded uses of therapeutic drugs and other chemicals in U.S. aquaculture. Ultimately, an efficacy and target animal safety testing process that focuses on the biological benefits and risks associated with treatment should result in the development and approval of more effective and safer aquaculture drugs and other chemicals, especially from an end-user's perspective.

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RELEVANT LITERATURE

The following is a list of journal publications with particular relevance to the broad topic of drugs and aquaculture species. This list comprises citations exclusively from 2009, 2010 and 2011. Please note that this list does not include those provided in previous issues of the AADAP Newsletter.

If you have come across literature that you believe would be of interest to the readership of the Newsletter, please forward the citation to Tom Bell (thomas_a_bell@fws.gov) and we will place it in the next edition.

The inclusion of a citation within the Newsletter does not imply: (1) recommendation of the technique to any particular situation, (2) concurrence with a treatment procedure/drug, (3) acceptance by the U.S. Food and Drug Administration's Center for Veterinary Medicine of the drug's safety or effectiveness, nor (4) in any way an endorsement of a product by the U.S. Fish & Wildlife Service.

Antibiotic and Bacterial

Avendano-Herrera, R, et al. 2011. Estimation of epidemiological cut-off values for disk diffusion susceptibility test data for *Streptococcus phocae*. *Aquaculture* **314(1-4):44-48**.

Chalupnicki, et al. 2011. Efficacy and toxicity of iodine disinfection of Atlantic salmon eggs. *North American Journal of Aquaculture* **73(2):124-128**.

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USGS's CORNER

Sedatives: The U.S. Geological Survey's Upper Midwest Environmental Sciences Center (UMESC) was asked by AADAP to evaluate the performance of a spectrophotometer method that is planned to be used to verify AQUI-S® 20E concentrations during animal safety and efficacy trials. UMESC conducted the evaluation according to FDA good laboratory practice (GLP) guidelines. The spectrophotometer method was accurate (>92%) and precise (<0.52%) when determining eugenol concentrations in AQUI-S® 20E solutions made in standard water (temperature ~20°C, pH ~7.5, and hardness ~170 mg per L as $CaCO_3$) and standard water with varying pH and hardness and nominal AQUI-S® 20E concentrations ranging from 50 µg per mL to 1000 µg per mL. The concentration range is most likely greater than the AQUI-S® 20E concentration range that will be used during impending AQUI-S® 20E target animal safety and efficacy studies. Contact Jeff Meinertz, jmeinertz@usgs.gov for more information.

Hydrogen Peroxide: UMESC submitted (14 April 2011) a final study report "Efficacy of 35% PEROX-AID® to control mortality caused by *Saprolegnia parasitica* or *Saprolegnia diclina* in walleye *Sander vitreum*" to CVM. The data summarized in this final report, combined with previous submissions (channel catfish *Ictalurus punctatus* and rainbow trout *Oncorhynchus mykiss*) may be sufficient to complete the effectiveness technical section to expand the current label for 35% PEROX-AID® for use in all species of freshwater-reared finfish to control mortality from saprolegniosis. Contact Maren Tuttle-Lau, mttuttle@usgs.gov, for more information.

Florfenicol: UMESC is gearing up to conduct a study that will provide the data to fulfill the following objectives: (1) determine the depletion rate of the florfenicol amine (FFA) residues from the fillet tissue of rainbow trout dosed with florfenicol (FFC)-medicated feed in a recirculating aquaculture system, (2) determine the FFC concentrations in the water of the recirculating aquaculture system during and after dosing rainbow trout with FFC-medicated feed, (3) determine FFA residue concentrations in the fillet tissue of non-dosed rainbow trout sharing a recirculating aquaculture system with rainbow trout dosed with FFC-medicated feed, and (4) determine the depletion rate of FFA from the fillet tissue of rainbow trout dosed with FFC-medicated feed in a flow through aquaculture system. The study is planned to begin during the mid to late summer of 2011, pending the outcome of CVM's Office of Minor Use Minor Species review of the request for funding submission. Contact Jeff Meinertz, jmeinertz@usgs.gov, for more information.

UMESC is also gearing up to conduct a pivotal efficacy study at the Spirit Lake Fish Hatchery (Spirit Lake, Iowa USA) to evaluate the effectiveness of florfenicol or oxytetracycline-medicated feed to control mortality from Motile Aeromonad Septicemia in muskellunge *Esox masquinongy*. This study is funded through interagency grant funds provided by the U.S. Department of Agriculture through its North Central Regional Aquaculture Center. Contact Maren Tuttle-Lau, mttuttle@usgs.gov, for more information.

Text provided by Mark Gaikowski, Fisheries Management Chemical and Aquaculture Drug Team, U.S. Geological Survey, Upper Midwest Environmental Sciences Center, La Crosse, Wisconsin, USA.

USDA's CORNER

Drew Mitchell receives award: Research Fisheries Biologist - Parasitologist, Andrew J. "Drew" Mitchell

(retired), ARS Harry K. Dupree - Stuttgart National Aquaculture Research Center, Stuttgart, Arkansas USA was honored with the S.F. Snieszko Distinguished Service Award on 16 June 2011 at the American Fisheries Society – Fish Health Section annual meeting in Nanaimo, British Columbia Canada. This is the highest award presented by the Fish Health Section, the purpose of which is to honor individuals for outstanding accomplishments in the field of aquatic animal health. His distinguished career includes significant contributions to fisheries and aquaculture.

Drew Mitchell on the left; photo courtesy of Dr. Mike Mauel, Mississippi State University.

Deborah Iwanowicz (U.S. Geological Survey's Leetown Science Center; Kearneysville, West Virginia USA) put it this way: "His practical approach to relevant issues in Southeastern warm water aquaculture perhaps sets him apart from typical fish health practitioners...His work has been selfless, focusing on helping the warm water aquaculture industry in regards to fish pathogen management...His contributions to the Fish Health Section are immense…"

Congratulations Drew on a well deserved honor.

Text provided by Dave Straus, Disease & Drug Approval Section, Harry K. Dupree – Stuttgart National Aquaculture Research Center (SNARC), Agricultural Research Service, U.S. Dept. of Agriculture, Stuttgart, Arkansas, USA.

MEETINGS, ETC.

UPCOMING MEETINGS

1st Australiasian Scientific Conference on Aquatic Animal Health; 5-8 July 2011; Cairns, Queensland, Australia: The conference, being held at the Pullman Reef Hotel, provides a forum for presentation of diagnostic, research, management and policy issues encompassing all areas of aquatic animal health and bio-security. Previously, the Aquatic Animal Health Subprogram (AAHS) of the Fisheries Research Development Corporation of Australia has organized national scientific conferences (in 2003, 2005, 2007 and 2009) featuring presentations on aquatic animal health research in Australia and an international aquatic animal health expert as the keynote presenter. While the format of the 2011 conference is likewise being hosted by AAHS, it is expected to be similar to previous conferences with an international keynote speaker, presentations on a range of aquatic animal health topics, prize for best student presentation etc., a recent decision was made to expand the conference to encompass the Australasian region, attracting participants from New Zealand, SE Asia and beyond. To receive the second conference announcement which will include the draft program, registration (registration fee will be Aus$330) and abstract forms and further accommodation details please provide Joanne Slater, FRDC Aquatic Animal Health Subprogram Coordinator (email: joanne.slater@csiro.au) with an expression of interest indicating whether you plan to attend and/or make a presentation (please indicate topic). Please provide the following details: your name, institution, postal address, email address, fax and telephone numbers. Also your area(s) of interest: research/management/ policy and regulation; finfish/crustaceans/molluscs/ reptiles/amphibians; viral/bacterial/parasitic/fungal pathogens; and/or diagnostic test development and diagnostics.

17th Annual Recirculating Aquaculture Systems Short Course; 11-14 July 2011; Ithaca, New York USA: This course is intended to give a thorough coverage of the design, operation, and management of water reuse systems for finfish (limited coverage of indoor shrimp production). This course is offered as a "hands-on" or a "distance learning" opportunity. Dr. Michael B. Timmons of the Cornell Aquaculture Program and Dr. James Ebeling of Aquaculture Systems Technology, New Orleans, LA) will teach the course. A combination of laboratory demonstrations and classroom presentations will be offered. At the conclusion of the workshop, individuals should be able to design their own water reuse systems and have a fundamental knowledge of the principles influencing design decisions. The following topics will be addressed. Water quality monitoring and measurement, engineering design of individual unit processes, system management, fish health management, economic and risk evaluation, tours of local aquaculture facilities (tentative) and indoor shrimp. For more information refer to the course website: http://tinyurl.com/6z72sfz

Salmon Disease Workshop; July 11-22, 2011; Corvallis, Oregon USA: This workshop is designed for professionals working in the fish health field and will emphasize recent advances and developments in our understanding of salmonid diseases. Specifically, the workshop will include sessions covering: current immunological and molecular techniques; sampling for pathogens in wild populations; new and emerging fish pathogens; cell culture techniques, including maintenance of cultures and viral identification; histopathology associated with salmonid diseases; current status of important viral, bacterial, and parasitic

pathogens; salmonid disease treatment practices in Pacific Northwest hatcheries; and epidemiology. The workshop is limited to 20 participants on a first come, first served basis. For more information, including lodging, registration, etc. refer to the following: http://tinyurl.com/47mfuuw.

Coral Tissue Slide Reading Workshop; 31 July - 5 August 2011, Mote Marine Laboratory; Summerland Key, Florida USA: This 5-day workshop focuses on the histology or microscopic anatomy of scleractinian corals, gorgonians, and other Cnidaria to support studies on their ecology, physiology, reproduction, biochemistry, systematics, molecular biology, genetics, immunology, embryology, and pathology. For more information refer to the course description webpage: http://tinyurl.com/4u8jbu6.

Diseases of Corals and Other Reef Organisms; 6 - 14 August 2011; Mote Marine Laboratory; Summerland Key, Florida USA: This course will introduce students to the field of pathobiology of marine organisms. The focus of lectures, dives, and laboratory sessions will be on diseases affecting hard corals, but diseases of other reef organisms will also be discussed. Methods of studying diseases will include collection of field monitoring data and physiological, histological and microbiological techniques. The course will provide students with a state-of-the-art overview of reef pathobiology, experience with relevant techniques, and an understanding of the need for a multidisciplinary approach to its study. For more information refer to the course description webpage: http://tinyurl.com/4827knc.

9th International Symposium on Reproductive Physiology of Fish; 9 - 14 August 2011, Cochin, India: This, the ninth meeting of this international group of scientist will be held at the Lulu International Convention Center and Garden Hotels. Sessions being planned for the symposium include topics on: reproductive neuroendocrinology, sex determination and gonad differentiation, reproductive strategies and sexual cycles, spermatogenesis, folliculogenesis, reproductive behavior and migration, reproductive toxicology, fish biotechnology and aquaculture. For more information refer to: http://www.9isrpf.org/index.html.

Health and Colony Management of Laboratory Fish; 15-19 August 2011; Mount Desert Island, Salisbury Cove, Maine USA: This is a novel short course to help technical staff, graduate students, postdoctoral fellows, junior faculty and investigators monitor the health of a colony of aquatic organisms. For more information refer to the course description at: http://tinyurl.com/28oamuo.

2011 International Aquaculture Biosecurity Conference and Workshop; 14 - 17 August 2011; Trondheim, Norway: The 2nd International Aquaculture Biosecurity Conference (14 - 15 August) will be followed by the 1st International Aquaculture Biosecurity Workshop (16 - 17 August). The Conference will cover the following topics: components of ideal biosecurity plans and programs; determining and mitigating critical control points and risks of disease introduction; surveillance, monitoring and determining disease status/freedom; diagnostic testing, veterinary and farm record keeping; national and international biosecurity strategies; contingency plans for the control and eradication of disease; immunoprophylaxis in biosecurity plans and programs; use of biosecurity manual for aquaculture (practical benchtop exercise); and biosecurity check list. The Workshop will allow for on-site review of the biosecurity practices throughout the entire value chain of seafood production, based on the current standard of the salmon aquaculture industry. For more information, including agenda, registration and lodging refer to their website: http://tinyurl.com/4m8zrsy.

AQUA NOR FORUM 2011; 17-18 August 2011; Trondheim, Norway: The European Aquaculture Society (EAS) in cooperation with the Nor-Fishing Foundation, SINTEF and CREATE, organizes this meeting that provides a forum for science, industry, consumers and policy makers to review developments in the aquaculture sector and to discuss the key issues that affect those developments. For more information please refer to the conference website: http://tinyurl.com/6hcmofo.

141st Annual Meeting of the American Fisheries Society; 4 - 8 September 2011; Seattle, Washington USA: The theme of this year's meeting is "New Frontiers in Fisheries Management and Ecology: Leading the Way in a Changing World," and is being held at the Washington State Convention Center. The official hotels for the meeting are the Seattle Sheraton, the Grand Hyatt Seattle and the Hyatt at Olive 8. The meeting will feature a broad range of technical, social, and legal topics that are of national and international

interest, including measures to recover from massive man-made and weather-related catastrophes and to ensure the long-term sustainability of fisheries resources. Regional topics will highlight efforts to protect and clean up Puget Sound and address emerging issues related to the Columbia River, salmon recovery, and watershed management. For further information, please refer to the meeting's website: http://afs2011.org/.

AQUACULTURE EUROPE 2011; 18-21 October 2011; Rhodes, Greece: The conference, organized by the European Aquaculture Society in cooperation with the Federation of Greek Maricultures (FGM), and Hellenic Centre for Marine Research (HCMR) will address vital questions affecting the development of Mediterranean aquaculture over the next decade, with reviews of the importance of aquaculture in EU food production; the sustainability of aquaculture feeds and the implementation of selective breeding strategies in aquaculture. A review of current EU-funded research programmes will highlight their relevance to the current and future production practices. The conference will include an international trade show, a Farmers' Day and a student workshop. It will also provide a platform to showcase European initiatives in aquaculture. For more information, please refer to the conference website: http://tinyurl.com/4q8dvbr.

Recirculating Aquaculture Systems: Design, Engineering, and Operation; 20-22 October 2011; Fort Pierce, Florida USA: This workshop is being conducted by, and held at, the Harbor Branch Oceanographic Institute at Florida Atlantic University. The course costs US$450 (until 10 October 2011) and provides in-depth training **on design, operation, and management of recirculating** systems for culturing fresh and saltwater species. Topics cover design criteria and system construction, water reconditioning and management of water quality, solids removal, disinfection, biofiltration, hydraulics, pump selection and aeration. The course provides practical considerations for stocking systems and developing feeding strategies. Topics include: overview of recirculation systems engineering, water quality and monitoring system components, engineering design of individual unit processes, system management, health management, and economic and risk evaluation. The minimum enrollment is 20 participants. Registration will be increased by U$50 if after October 10th. For more information refer to Harbor Branch's website: http://tinyurl.com/6gltg7v.

VIII International Symposium on Fish Parasites; 26-30 September 2011; Viña del Mar, Chile: This year's Symposium will be an important forum for the discussion and distribution of new findings in this rapidly expanding field. The theme of the conference is "Fish Parasitology: from Classical Taxonomy to Holistic Approach". The organizers hope to develop an exciting scientific program that will provide an update in our field of research. They are sure that the diversity of themes in the dynamic field of fish parasitology will be the most favorable platform for strong and positive collaborations between fish parasitologists. An intense program is scheduled to include preliminary talks, mini symposiums, and oral presentations. Poster sessions will be an important aspect of 8th ISFP. Competitive awards for students and postdoctoral scientists from developing countries will be offered. In addition, a diverse and enjoyable program of social activities will also be provided in order to showcase the best of Chilean traditions and culture. See the conference website at: http://www.8isfp.com/.

8th Symposium on Diseases in Asian Aquaculture; 21-25 November 2011; Mangalore, India: The DAA8 is being held at the Hotel Moti Mahal in the heart of Mangalore, India. The conference is being sponsored by several groups including the Asian Fisheries Society (AFS) and the Fish Health Section of AFS. For more information refer to the conference website: http://www.daa8.org.

3rd International Symposium on Cage Aquaculture in Asia; 16 - 19 November 2011; Kuala Lumpur, Malaysia: This year's symposium will be held at the Putra World Trade Centre in conjunction with Malaysian International Seafood Exposition 2011. The symposium is scheduled to include topics/ sessions covering: site selection and environmental management (including adaptation to climate change); species selection and seed production; feeds and feeding; biosecurity and health management; production technology and systems; economics, markets and certification; and policy and regulations. Additionally there will be a special sessions on seafood trade and

certification and farmers' day. For additional information visit the symposium website at: http://tinyurl.com/48lkyac.

CVM's NOTES

Drug Short-Course Lectures Available Online: The American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) sponsored a Veterinary Drug Regulatory Life Cycle Course on 28 February to 4 March 2011.

The course, taught by CVM staff, was targeted to industry and academic stakeholders interested in understanding the regulatory science behind veterinary drug development. It provided an overview of current FDA CVM policies, procedures, and standards for pre- and post-approval requirements in the veterinary drug life-cycle.

A video of each lecture presented during the course is available online (http://tinyurl.com/633zw6u).

eSubmitter and the Electronic Environment: As mentioned in the November 2010 AADAP Newsletter, CVM developed a tool to enable the animal drug industry to voluntarily submit all submissions to CVM electronically. The tool has been active since March 2011 and can be downloaded from the CVM website (http://tinyurl.com/6jtkx7g). To use eSubmitter, a gateway account is required with FDA/CVM. For information on how to set up a gateway account, please visit the FDA's gateway information page (http://tinyurl.com/yj98wqs) or view Sarah Bembe's presentation from last year's Aquaculture Drug Approval Coordination Workshop (http://tinyurl.com/6znrnwx). CVM requests that participants who use eSubmitter submit all submissions through eSubmitter and no longer submit paper submissions to CVM. Furthermore, if a submission comes in via eSubmitter, its amendments must also be submitted via eSubmitter; if a submission comes in paper, its amendments should be submitted in paper. eSubmitter participants will receive all CVM correspondence through the gateway electronically (no paper letters will be mailed).

With the launch of eSubmitter, the SmartForms currently available on CVM's website (http://tinyurl.com/6jtkx7g) will not be accessible or accepted electronically beginning October 2011 since the information captured by the SmartForms is received in the eSubmitter submissions. If you are currently printing and submitting the SmartForms in paper, you will need to save the form for future use or record the requested information in a different format for submission to CVM.

Those who are not ready to submit electronically can continue to submit paper submissions. Once CVM receives the paper submission, their Document Control Unit (DCU) will scan the submission for electronic review. Due to the new scanning procedures, sponsors only need to send **one** paper copy of their submissions instead of the previously required three. Participants who submit paper submissions will receive a paper response letter in the mail from CVM.

Questions and comments regarding these new procedures can be addressed to Sarah Bembe (sarah.bembe@fda.hhs.gov, 240.276.8346).

Grants: Applications for MUMS grants to defray the cost of pivotal safety and effectiveness studies are being accepted now through 5 August 2011. Only new animal drug products that have been designated by the Office of Minor Use and Minor Species are eligible, and there must be protocol concurrence from the Office of New Animal Drug Evaluation for the study proposed for grant funding. Detailed information is available at this website link (http://tinyurl.com/y2mbmvm) and applications must be submitted electronically through Grants.gov (http://grants.gov). Please contact Dr. Joan Gotthardt (joan.gotthardt@fda.hhs.gov) if you have any questions.

Staff at CVM: We are pleased to announce that Adrienne Kurtz joined the Aquaculture Drugs Team (Office of New Animal Drug Evaluation) this past November.

Please note also that Dr. Scott Melton (scott.melton@fda.hhs.gov, 240-276-8666) is the new contact for aquaculture and import tolerance issues in the Office of Surveillance and Compliance.

Text provided by Drs. Jennifer Matysczak and Sarah Bembe, Aquaculture Drugs Team; Office of New Animal Drug Evaluation; Center for Veterinary Medicine, Food and Drug Administration; Rockville, Maryland USA