U.S. Fish and Wildlife Service — Fish and Aquatic Conservation

AADAP NEWSLETTER

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"

Summer 2016 Vol 12 Issue 1

Summer time in the South Cottonwood Drainage, Bozeman, Montana

AADAP/USFWS

In this Issue

21st Annual Aquaculture Drug Approval Coordination Workshop – Overview

The 21st annual Aquaculture Drug Approval Coordination Workshop was held in Bozeman, MT on July 28-30, 2015. When we started putting things together for the workshop back in March, like sketching out the agenda and laying out the general meeting logistics, we discussed that the agenda might not cover two full days because fewer research entities than in the past are currently dedicated to fish drug approval research and associated activities. We also estimated that attendance would be around 50 because of tightening of the old budget-belt. Turns out we were a little off on both accounts – we could barely squeeze everything in that ended up on the agenda, and attendance hit 70. As we've done in the past, the meeting started off with a 5,000 ft elevation perspective of the overall drug approval effort with presentations by Ryan Roberts (AFWA National Fish Habitat Action Plan Communications Coordinator), Steve Sharon (Chair - AFWA Drug Approval Working Group), and Dave Miko (USFWS Headquarters Office). We then launched into 1.5 d of technical presentations, drug approval research updates, status reports on new expanded drug approvals, and updates from several of the CVM Teams that were in attendance. Along the way there was a lengthy set of presentations and discussion regarding the use of Draxxin (an antibiotic approved for use in cattle and swine) to control mortality due to bacterial kidney disease in Chinook salmon, and the use of strontium chloride as a skeletal marking agent on Pacific Salmon.

We understand that there are demands on everybody's time, and there are typically more meetings or workshops that one would like to attend than is possible. For that, we were very appreciative that the meeting was so well attended, that Dave Miko from the USFWS Headquarters Office could attend, that we had a number of potential new sponsors in attendance, and that once again everybody survived the decompression float trip without serious mishap!

The meeting would not have been possible without the generous contributions of the following sponsors: FishVet Group; PharmGate Animal Health; Aqui-S New Zealand, Ltd.; Aquatic Life Sciences/Western Chemical, Inc./ Syndel Laboratories, Ltd.; Merck Animal Health; Phibro Animal Health; AquaTactics Fish Health; Solvay Chemicals ; American Fisheries Society Fish Culture Section; and the Association of Fish and Wildlife Agencies. A BIG THANKS to all!

2015 Aquaculture Drug Approval Coordination Workshop attendees posing for a group photo on the shores of Hyality Reservoir, Bozeman, MT.

AFWA Drug Approval Working Group and Aquaculture Drug Approval Coalition Meeting – Overview

DAWG

The annual AFWA Drug Approval Working Group (DAWG) meeting was held on Wednesday, February 24 at the Paris Hotel Las Vegas in conjunction with the 2016 World Aquaculture Society Conference. Attendees included DAWG Chair Steve Sharon and six voting members (Dave Erdahl/USFWS, Jeff Meinertz/USGS, Dan Mosier II/KansasW&P, Katie Haman/Washington DF&W, Alan Johnson/Iowa DRN, Clint Peacock/Georgia DNR). In addition, a number of non-voting attendees representing USFWS, USDA-ARS, FDA CVM, Texas P&W, Idaho DF&G, and various drug sponsors participated in the meeting. The focus of the meeting was to discuss the status of fish drugs that are in the approval pipeline and to reclassify their priority (Tier I, II, or III) if necessary. In addition, it was noted that Clint Peacock is a new member representing Southeast US and the Gulf Coast of the U.S., and that Katie Haman is now the DAWG co-chair and will be phased into her new role as Steve Sharon's role phases out as he gets closer to retirement. Below is a brief recap of each drug discussed:

Tier I Drugs

Hydrogen peroxide (35% Perox Aid)

Sponsor is dealing with issues related to the manufacturer and supply. Currently trying to line up a new manufacturer and availability of product is dependent upon Emergency Drug Shortage requests by the sponsor. Progress to expand the current 35% Perox Aid label to include treatment of *Gyrodactylus spp*. in salmonids is on hold until issues related to a new manufacturer have been resolved. The sponsor has been in discussion with CVM requesting a new manufacturer site approval and for approval to package product in 5-gal buckets, and noted that Post-Approval changes require substantial time and resources to complete. The DAWG voting members voted to move hydrogen peroxide from a Tier I to a Tier II drug.

Eugenol (AQUI-S20E)

Sponsor provided an update on the status of technical sections and that they are still on track for an initial approval to sedate freshwater salmonids to handleable in early 2017. The effectiveness and target animal safety technical sections are complete for all freshwater fish. The study by the USGS Upper Midwest Environmental Sciences Center to determine depletion of eugenol from rainbow trout tissue has been completed and the report has been submitted to CVM. Plans are in the works to conduct similar studies with non-salmonids. All environmental studies (toxicity studies on algae, daphnia, and fathead minnows, a demineralization study, and an absorption/desportion study with five different soils) have been completed and reports submitted to CVM. If all are acceptable to CVM, then the sponsor will begin drafting the Environmental Assessment. The sponsor is also working on the Chemical, Manufacturing, and Control package and has indicated that it will be submitted to CVM for review in 2016. If all goes according to plan, then an early 2017 initial approval is realistic. An approval for all freshwater finfish will take another year to complete based on the need to complete additional eugenol depletion studies. Efforts are underway to generate data to support an approval for the use of AQUI-S20E to sedate marine fish to handleable in a seawater environment and five effectiveness studies have been completed so far on pompano (two life stages), cobia, black seabass, steelhead trout, and sablefish. A protocol to evaluate the effectiveness of AQUI-S20E to lightly sedate salmonids was developed and accepted by CVM, and MUMS grant applications were submitted in December 2015 to conduct light sedation trials on rainbow trout, cutthroat trout, and Chinook salmon. AADAP will hear back from the MUMS office in May, 2016 whether or not the grants were awarded. Lastly, a revised white paper was submitted to CVM's Human Food Safety Team requesting immediate-release status for use of AQUI-S20E for sedation of marine fish in a seawater environment. Expanding the initial label for light sedation and sedation of marine fish will require additional studies to support immediate release.

Chloramine-T (Halamid Aqua)
The sponsor is still looking for a new source of chloramine-T and are hopeful that the company that they are now working with will be on board by June 2016. At that time, they will begin the process to complete their CMC package so that Halamid Aqua can once again be sold legally in the U.S. for use on fish. All chloramine-T that had been available from an Emergency Drug shipment has been exhausted and each new request has to be authorized by CVM. It was recommended that chloramine-T remain a Tier I drug for the time being.

Emamectin benzoate (SLICE)
The sponsor stated that the company intends to pursue one or more aquaculture claims and wants to meet with AADAP staff to discuss the status of the initial approval(s) through a formal meeting.

Tier II Drugs

Oxytetracycline hydrochloride (Pennox 343)
The sponsor is committed to relabeling the product due to impending changes to regulations where over-the-counter drugs would become Veterinary Feed Directive drugs. As per a request from CVM, AADAP has developed a dose-ranging testing protocol that has been submitted to CVM for review. The focus of these studies is to test OTC-HCL doses ranging from 40 to 100 mg/L to find the lowest dose that consistently controls mortality in fish due to a variety of fish diseases (i.e., coldwater disease, columnaris). Things required for traditional field effectiveness protocols such as dose verification, will not be required under this protocol. If the protocol is approved, MUMS grant funding would be potentially available.

Oxytetracycline dihydrate (Terramycin for Fish)
The sponsor is reformulating the product and drafting a new label to comply with the new VFD regulations. The sponsor would be willing to conduct or support conduct of additional effectiveness studies if no extra-label use is allowed for VFDs. AADAP would be willing to conduct skeletal marking studies on non-salmonids if the sponsor is willing to expand the label to allow such use.

Copper sulfate
Dave Straus stated that the initial approval will be for treatment of *Ichthyophthirius spp.* on catfish in earthen ponds and fungus on catfish eggs, and that he will ask folks at CVM what additional data would be needed to expand the proposed initial claim to include treatment for columnaris on catfish. All technical sections have been completed for the initial claim with the exception of the Environmental Assessment. Dave has worked to line up a new sponsor (Chem One), and is working with them to schedule a product develop meeting with CVM, and will be asking the Environmental Safety Team for help completing the EA. Dave expressed concern that identical bags of copper sulfate from Chem One will have one of two different labels, depending upon with it's to be used as an FDA-approved product or an EPA-registered product.

Diquat
AADAP request a slaughter-authorization, but will not hear back from CVM on this request until June. Three companies have expressed an interest in sponsoring diquat.

17 alpha-methyltestosterone
A bona fide source of 17MT has been found and CVM's Environmental Safety Team has started the Environmental Assessment. Other fish producing groups are also interested in availability of an FDA-approved 17MT product, but efforts will remain focused on use on tilapia. AADAP was contracted by a third-party and recently developed and submitted a TAS protocol to CVM for use on rainbow trout; there are no immediate plans to conduct any such study. Steve Sharon will ask CVM to review approvals based on dosage rate rather than species. It was agreed to move 17MT to a Tier I drug.

Tier III Drugs

Erythromycin

There might be a new sponsor available for erythromycin, particularly the injectable form. Doug Munson will be sending around a survey to gather information on potential use.

ADAC

This group serves as an advocate for the advancement of aquatic drugs for fish culture and fisheries management activities. It is intended to develop and maintain a concerted voice bringing together representatives from the various factions of the aquatic drug approval arena: state and federal partners, fisheries organizations, drug sponsors, and the private aquaculture industry. The group met immediately after the February 24th DAWG meeting and discussed the following issues:

1. Forming a working group to voice concerns and ask CVM questions regarding the upcoming changes to Veterinary Feed Directive regulations. The working group will consist of Jen Matysczak, Pat Guant, Kasha Cox, and Jim Brackett. Specifically, the group will ask questions such as how will Type B medicated feed products be handled and clarifying FDA's definition of "top-dressing" and "top-coating" feed. Jim Brackett will bring this issue up with the AVMA on their March 27, 2016 meeting.

2. Survey private aquaculture to assess their disease concerns and fish drug needs. AADAP will take the lead on developing a survey. Have asked Carol Engle and her PhD. student Johnathon Van Senten for help, but will unlikely be able to pay the consulting fee. Intend to have a draft survey out in April and ready for distribution in May.

3. AADAP funding – discussed the importance of AADAP's continued role in the overall US drug approval effort; Strategies to maintain/increase funding support be discussed and handled by several individuals.

4. Offshore aquaculture – discussed problems associated with offshore aquaculture and the lack of jurisdiction and veterinarian licensing, such as how a veterinarian would go about prescribing approved drugs extra-label.

Healthy LMB at Richloam Fish Hatchery, Florida after treatment with CHLT.

USFWS INAD UPDATE

2015 INAD Statistics

In 2015 the National INAD Program once again had another very successful year! We had a total of 211 federal, state, private, tribal, and university facilities participating in the program. These facilities were enrolled in 263 individual INAD sign-ups, with Aqui-S® 20E leading the enrollment numbers followed by Aquaflor® and LHRHa. The INAD participants kept all of us busy last year with 763 different study numbers requested!!

2016 INAD Program Participants

Sign-ups for the 2016 INAD Program are under way, and invoices are being sent out to all non-USFWS participants enrolled in the program. **Please remember that enrollment and study numbers do not automatically carry over from the previous year.** If you find that you are unable to create a study request or enter a drug receipt, please check your investigator Account Info section to make sure the 2016 enrollment has been added to your account.

INAD Report Review

There is currently a large number of INAD studies in stage 6 waiting review by AADAP. Once your study has reached stage 6 there is nothing more you need to do. Once I am able to review your study I will contact you if I have any questions. Otherwise, anticipate that your study will be advanced to stage 7 soon!

Website Updates

We have been able to update our website as needed. Please be sure to review the INAD fact pages and INAD study protocols. We also have a link to the AADAP Flickr album, so be sure to check this out. Be forewarned: We are looking for any-and-all INAD related pictures that you may have. If you have any pictures that you are willing to share, please contact Bonnie Johnson so that we can get them posted. We have also added an "Our Fans" section under the Resources button on the AADAP website. In this section we will be posting INAD related articles or feedback we receive from the field.

NADA MANAGEMENT UPDATES

What's good for the goose is good for the gander. In this case, what's good for use of AQUI-S® 20E in freshwater is good for use in seawater. As some of you may recall, researchers with the USGS Upper Midwest Environmental Sciences Center (UMESC) submitted an excellently prepared document to support selection of appropriate exposure criterion to assess the potential risk to humans from consumption of fish tissue containing residues of AQUI-S® 20E. The document described (1) the need for immediate-release sedative for fish, (2) the components of a risk analysis process to evaluate the risk of human consumption of recently sedated fish, (3) information to describe the probability of fish being sedated by fishery management scientists, (4) information to describe the probability of recently sedated fish being harvested by anglers, and (5) a risk analysis of the probability of fish sedation coupled with the probability of angler harvest. Additionally, they concluded that what they provided would support a conclusion by FDA that a safe sedative residue limit for the edible tissue of freshwater fish would be best modeled through the calculation of an Acute Single Daily Intake (ASDI). What does this all mean? It means that if FDA accepted this model, then AQUI-S® 20E could be used in the field as an immediate-release sedative in the absence of the remaining mammalian toxicology studies. These studies, which would have to be paid for by the sponsor, are very, very, very expensive and the sponsor is not in the position to fund them at this time. Due to the excellent work by the UMESC staff, FDA concurred that the information and data provided does support an ASDI. Upon hearing the good news, AADAP staff quickly requested that CVM allow AQUI-S® 20E to be used as an immediate release sedative for field use on freshwater fish.

Availability of an immediate-release sedative has been a blessing for fisheries managers, field biologists, and researchers who need to sedate freshwater finfish during the course of their work. It wasn't long before those doing similar work on marine fish inquired whether the immediate-release status extended to sedation of fish in a saltwater environment. Alas, the answer was no. As a result, it was time for us to use the strategy that UMESC successfully used, and provide information to CVM's Human Food Safety Team to support use of AQUI-S® 20E as an immediate-release sedative for field work in salt water environments. We took a stab at it and developed a document that described (1) the need for an immediate release sedative for freshwater and marine fish, (2) U. S. marine recreational and commercial landings and species likely to be treated with AQUI-S® 20E for fisheries management activities, and (3) area of total inland waters and oceanic waters. We found that there is a paucity of tag and recapture data relative to marine fish and very little evidence that captured fish were sedated. The numbers we came up with showed that recapture rates were low and time at liberty was pretty lengthy. In a letter submitted to CVM in early June, we requested that FDA agree that an ASDI is appropriate to protect human health associated with the use of AQUI-S® 20E on fish sedated in a marine environment for fisheries management purposes. Alas, we received a letter from CVM in September requesting additional information to help them determine if human consumption of fish immediately released after sedation for fishery management activities in the marine environment can be considered a rare occurrence. Specifically, they requested additional information on (1) capture methods and efficiencies for marine fishes in field studies, (2) capture methods used in the in-shore zone of different geographic marine bodies of water, (3) differences in the needs of sedative use between oceanic and inland field studies (if exists), and (4) provide references for recapture rates for striped bass and white seabass in California we referenced in the original submission. The original submission was revised, we tried our best to provide them with the requested information, and we included two new sections: (1) capture methods and efficiencies for marine fish, and (2) tag and recapture studies of marine fish and sharks. The revised submission was submitted to CVM on January 11, 2016, and we hope the 2nd time is the charm.

Update From World Aquaculture Society 2016

Aquaculture America 2016 was held Feb 22-26, 2016 at the Paris Hotel and Convention Center in Las Vegas, Nevada - and it was a doozy. It was one of their largest meetings ever with over 2,400 attendees, 1,000+ oral presentations spread over 83 symposia and 13 daily concurrent sessions, 190 posters, and their largest trade show ever with 156 vendors. Some of the symposia that we found most interesting this year included the 1) Effects of the Regulatory Environment; 2) Fish Welfare; 3) Physiological Insights Towards Improving Fish Culture; 4) Aquaculture in California; 5) Permitting Aquaculture in the Gulf EEZ; 6) Marine Aquaculture in a Changing Environment; 7) Influence of Activists and Media Innovation in Aquaculture Production; and the ever-popular but unpredictable 8) Federal Town Hall Meeting. Whether you moved from room-to-room to try to catch what you might consider the presentations that best suit your interest, or sat-tight through the bulk of a particular symposium, there were plenty of good presentations to choose from. As usual and as is typical, there was also lots of action/discussion going on outside of the presentation rooms (*see Meetings during the Meeting below*), and we took full advantage of the fact that virtually all the drug sponsors we work with were in attendance. Dave Miko (USFWS Chief of the Division of Fish and Aquatic Conservation) was also in attendance, and we did our best to introduce and familiarize Dave with the many "players" in the aquatic species drug approval arena. All in all, it was a GREAT meeting!

Meetings during the Meeting

Before heading out to Las Vegas, we reached out to a number of fish drug sponsors and scheduled time for meetings to discuss 1)what they were up to; 2) what AADAP was up to; and 3) how we could best work together to move our mutual objectives forward. All-in-all, things could not have worked out better. We met first with Solvay Chemical's Alastair McNeilllie and some of the folks he is working with to discuss their products. They are working towards a path for an initial approval with their 50% hydrogen peroxide product, and are also open to supplemental approvals with this or other products. The upshot for AADAP is that it's likely we'll have another INAD (50% H2O2) to administer, and we are optimistic that there will eventually be opportunities to pursue MUMS grant funding for future 50% H2O2 research.

We had multiple discussions with our longtime collaborator Dr. Dick Endris (ex-Merck Animal Health and currently President of Endris Consulting,

Happy, healthy Rainbow Trout!

Inc.), who was at AA2016 representing a number of drug companies including Pharmgate (Pennox® 343), Axcentive SARL (Halamid® Aqua), and Phibro Animal Health (Terramycin® 200 for fish and 17a-methyltestosterone). We have a number of studies lined-up with Pennox® 343, and are hopeful that the efficacy work will lead to supplemental therapeutic label claims. We discussed Halamid® Aqua supply issues (i.e., a lack thereof), and unfortunately concluded that this is likely going to be an on-going problem in the near-term. However, please be aware that all involved are doing everything possible to rectify this situation at the earliest possible date.

We were brought up-to-speed on the initial approval of AQUI-S® 20E during our meeting with Dr. Tom Goodrich, who was there representing AquaTactics and Aqui-S New Zealand. There continues to be considerable interest in the use of AQUI-S® 20E in both field and hatchery programs, and Tom reported that best case scenario we're about 12 months away from an initial approval. FDA-boxes have been or are getting checked off relative to environmental safety, residue depletion in trout, and chemistry and manufacturing. This was pretty darn exciting news! It's surprising how many people we talk to who are still out there using things like Alka Seltzer to sedate fish, but rest assured these folks are just as anxious as we are for AQUI-S® 20E to be approved.

We had a great meeting and discussion with Etan Bendheim and Dr. Raanan Ariav from Phibro Animal Health - and yes, Dr. Endris was present as well! There are some very cool things going on with Phibro, and we're excited to be partnering up with this company to bring some new aquaculture drugs to the medicine chest. Most of our discussion centered on the final steps necessary for the approval for 17a-methyltestosterone medicated feed for use to sex-reverse larval fish, as well as early-stage efforts exploring the possibility of an approval of a new, potential aquatic species antibiotic.

Lastly (but my no means leastly), we met with Dr. Jim Brackett and Dr. Peter McKenzie(Western Chemical, Inc./ Syndel Laboratories/Aquatic Life Science) to talk about some of their products. We later met with Jim and one of the researchers he's been working with to discuss generating the type of data required by CVM to demonstrate safety and effectiveness. All we can say after that meeting was that it couldn't have gone more smoothly. One of the first things we did when we got back to Bozeman was to start getting some product information so that we can begin to develop research efficacy and target animal safety protocols for one of their products. If the success of a meeting is demonstrated by how much more work you've got lined up after the meeting as compared to before, this was a VERY successful meeting. Yes, we are being somewhat coy about the specifics of this meeting, but suffice it to say that we have already submitted a study protocol to FDA with respect to one of these products, and have requested a new INAD authorization for another…..forward movement….we love it!

Keeping an Eye on the New Guy

It was our pleasure to "host" Dave Miko (USFWS - Chief of the Division of Fish and Aquatic Conservation) at his first Aquaculture America meeting. Dave came to the FWS a couple of years ago after a lengthy and storied tenure with the Pennsylvania Fish and Boat Commission and immediately inherited, amongst other duties, the daunting task of providing HQ-level oversight of AADAP – a band of known rebels with a singular cause. Notwithstanding our fanatical desire to somehow "win" in the treacherous drug approval game, nearly from the git-go Dave has been a staunch advocate for AADAP. Of course we were not really hosting Dave, but it was our pleasure to have the opportunity to hang out with him at such a premier venue (no, not Las Vegas, AA 2016)….and to help provide him with a better perspective of the true "breadth and scope" of the collaborative aquatic species drug approval efforts. Our thanks for the many partners who not only helped to further Dave's drug-education, but also showed him true "family hospitality." It was simply an added bonus for us that quite a number of folks came up to us during the meeting and let us know that they were pretty doggone impressed with our Boss - that he certainly appeared to be genuine, sincere and trustworthy, and overall, a great representative for USFWS as we all look to the future. And hey, that's pretty high praise for any Federal employee!

AADAP Drug Updates

Most baby-boomers know of Mighty Mouse, an American animated superhero mouse character created by the Terrytoons studio in films that appeared on American television from 1955 through 1967 on Saturday mornings. Although nothing we do makes it on television, we can sort of relate to Mighty Mouse - we may be small, but we like to think we're mighty, and doing a mighty fine job at developing research protocols and generating data to support fish drug approvals in the United States. This past year we received some good news from CVM regarding concurrence of pivotal study protocols and final study reports, and we were also informed by CVM that we had to provide them with additional information for concurrence on other submissions. At the end of the day, we want to move the needle, even if it's just a little nudge. If that means not getting concurrence on the first go-round, we have come to accept that. We just add a new project to our "to-do" list, revise the document, and resubmit to CVM. Here's what's been going on since the last Newsletter:

Pennox®343 (75.6% oxytetracycline hydrochloride)

In the last newsletter, we described two trials that we coordinated with the Florida Bass Conservation Center in Webster FL to evaluate the effectiveness of OTC-HCL immersion therapy to control morality associated with columnaris in bluegill (one trial using 20 mg/L OTC-HCL and the other using 50 mg/L OTC-HCL). After the dust had settled we concluded that neither trial worked out and would have to be repeated. CVM expressed their concern that we had not adequately characterized the effective dose. Although there were some extenuating circumstances with the study design (i.e., fish were stocked in test tanks at densities much lower than that in the reference tank leading to potential spontaneous recovery), this was one of those times where it was difficult to disagree with CVM's assessment with respect to inadequate dose characterization. We had several discussions with CVM's Aquaculture Drugs Team and discussed the existing paucity of dose characterization data, the challenge of putting all of our eggs in one basket when it comes to selecting a therapeutic dose, and that without additional (i.e., new) MUMS grant funding we'd likely not be able to conduct the necessary dose characterization studies. The solution that CVM came up with is truly novel – develop a dose characterization protocol that can be submitted to the Aquaculture Drugs Team for concurrence, which will allow us to fulfill at least one of the criteria to compete for MUMS grant funding. Furthermore, they requested that we not go into such detail with these "pilot study" protocols and design them to capture as much pertinent info as possible relative to a truly therapeutic dose. We are in the process of stripping the current CVM-approved protocol entitled: The Efficacy of Pennox 343® (oxytetracycline hydrochloride) Administered as a Static Bath to Control Mortality of Freshwater-Reared Finfish" and rebuilding it to provide CVM with the dose characterization information they are looking for. Because this is the first attempt at this type of protocol, we're going into this realizing that the first-time submission likely won't "be a charm," and we will need to work with CVM via the End Review Amendment process to achieve the desired product.

We also received a bit of good news from CVM. They concurred that the results from a study we conducted to evaluate the Efficacy of PENNOX®343 administered as a static bath to control mortality of large fingerling rainbow trout *Oncorhynchus mykiss* caused by bacterial coldwater disease (BCD; causative agent *Flavobacterium psychrophilum*) was successful. Furthermore, they found the study was acceptable to support the effectiveness of oxytetracycline hydrochloride for the proposed indication when administered as a static bath at a dosage of 49 mg/L for 60 minutes on three consecutive days. They did however point out that the effectiveness technical section remains incomplete for the proposed indication until we provide them with data from one additional successful study. Here's where we could have used a bit of karma, but no such luck. For more information on this study, check out AADAP Drug Research Bulletin #47 (http://www.fws.gov/fisheries/aadap/PDF/Publications/DRIB_47_Pennox343-columnaris-BLG_final.pdf).

Subsequently, we did conduct a second study with Pennox 343 to control mortality associated with BCD - this time using cutthroat trout as the test animal. We worked hard at trying to get them sick and when they finally broke, we thought we were home free. Unfortunately, things were not looking too bright as the study progressed as a result of a very high level of daily mortality in ALL tanks. At the end of the 14-d posttreatment period, virtually every fish in every tank had died. We worked closely with the FWS Bozeman Fish Health Center staff trying to determine the primary cause of mortality. It was found that although *Flavobacterium psychrophilum* was detected and confirmed in fish sampled during the acclimation period and during the treatment period, it was not detected during the posttreatment period. We did a lot of head scratching on this one, suspected that there might have been water quality issues involved, and are currently in the process of writing up a brief report to submit to CVM. It'll be back to the drawing board for this one.

Halamid Aqua (chloramine-T)

In the last newsletter, we reported that we (AADAP and the good folks with the NY Department of Environmental Conservation) were successful in demonstrating the effectiveness of chloramine-T to control mortality associated with columnaris disease in Tiger Musky. Results from the study, which was conducted at the S. Otselic Hatchery, were written up and the final study report submitted to CVM in June 2015 for review. On July 10, 2015, we received word from CVM that the technical section is complete for the use of Halamid Aqua (chloramine-T) for "*the control of mortality due to external columnaris disease associated with Flavobacterium columnare in freshwater-reared coolwater finfish when administered at a concentration of 20 mg/L in a continuous flow water supply or as a static bath once per day for 60 minutes on consecutive or alternative days for three treatments*. That, my friends, is good news!! We're hopeful that the sponsor will take the next step and get this new claim on the label. For more information about this study, check out AADAP Drug Research Bulletin #46 (http://www.fws.gov/fisheries/aadap/PDF/Publications/DRIB_46_CLT-columnaris-TIM.pdf).

AQUI-S® 20E (10% eugenol)

Light sedation - Preliminary testing does pay off. In the last newsletter we described our efforts to develop a protocol to evaluate the effectiveness of AQUI-S® 20E to lightly sedate freshwater salmonids for purposes such as pre-transport loading, grading and sorting, staging broodstock, and transporting fish at low densities. It's one thing to propose to collect lots of data during very short periods of time (i.e., during the first 15 min of light sedation study), but it's quite another beast to verify that it can be done. Upshot: we were able to conduct a full-on preliminary study confirming that we were proposing could in fact be accomplished, and proceeded with confidence that what we were sitting on a good protocol. Reviewers with CVM's Aquaculture Drugs Team concurred, and the protocol was accepted on September 9, 2015. With a CVM-accepted protocol in hand, we plan to conduct studies on rainbow trout, cutthroat trout, and possibly Chinook salmon to generate sufficient data to support a claim of light sedation for all freshwater salmonids. Stay tuned!

Marine fish sedation to handleable – We have tested five different marine fish species in six different trials. In August/September we were hosted by Dr. Mike Schwarz and Steve Urick at the Virginia Seafood Agriculture Research and Extension Center (Hampton, VA) to sedate small and large fingerling Florida Pompano and fingerling cobia. When we wrapped-up this effort, we drove an hour east and were hosted by Chris Bentley, manager of the Bradford Bay Hatchery (Quimby, VA) to sedate juvenile Black Seabass. In November we were hosted by Chris Tartara and a host of others at the NOAA Manchester Research Station (Port Orchard, WA) to sedate juvenile steelhead trout and sablefish.

In the studies conducted on the East coast, fish were sedated to handleable with AQUI-S®20E at 30 mg eugenol/L or 120 mg/L tricaine methanesulfonate (active control). We tested 30 mg eugenol/L because it is likely the lowest efficacious dose that might be used on marine fish reared or held in warm water (i.e., ~25°C). A fish was determined to be handleable when it lost equilibrium and the ability to swim, could easily be caught and held by hand, and did not struggle while being weighed or measured. All fish became

handleable within 4.9 min (mean times ranged from 0.8 to 2.1 min) and recovered from sedation within 17 min (mean times ranged from 4.3 to 6.2 min). For more information on these studies, check out DRIB #48 (http://www.fws.gov/fisheries/aadap/PDF/Publications/DRIB_48_Sedative-eff-warmwater-marine.pdf).

In the studies conducted at NOAA's Manchester Research Station, sablefish were sedated with AQUI-S®20E at 60 mg eugenol/L to the handleable stage of anesthesia, and mean times to sedation and recovery were 1.6 and 7.3 min, respectively. Steelhead trout were sedated with AQUI-S®20E at 25 mg eugenol/L to the handleable stage of anesthesia, and mean times to sedation and recovery were 1.7 and 4 min, respectively. No fish died in either study.

Final study reports have been written and submitted to CVM for each of the studies described-above. Based on our experience conducting similar studies on freshwater fish that that have be submitted to CVM, we are pretty confident that these studies on marine fish will also accepted. However, and also based on our experience, it's better to wait to hear back from CVM than to put all of the eggs in the "it'll be accepted" basket. We should hear back from CVM in June 2016 whether or not the studies were accepted. If they are all accepted, we figure we're about ½ way to completing the effectiveness technical section for an "all marine fish handleable claim."

17-alpha methyltestosterone (17MT)

At the behest of folks within the commercial industry, we were asked to develop a study protocol to evaluate the safety of 17MT medicated feed fed to rainbow trout fry. We coordinated with Ralph Elston and folks at Trout Lodge Inc. to obtain the treatment specifics with respect to an effective treatment regimen to produce 'masculinized females' for the purpose of facilitating the elimination of genotypic males from the brood stock. Fertilization of females is then accomplished with masculinized females that produce sperm containing no Y chromosomes. Administration of methyltestosterone has been shown to be an effective method for sex control of salmonid fish. It is particularly useful for the production of all female fish because drug administration occurs at an early life stage of the brood stock rather than in a fish that may be stocked in public waters or processed for human consumption. Based on our previous experience developing a similar protocol for use in early life stage tilapia, we're pretty confident that we've developed a protocol that should be acceptable, or nearly so, to CVM. The protocol was submitted in early December so we should be hearing back any day now as to whether it's been accepted, or perhaps in need of "minor adjustment" via the End Review Amendment process.

DOING OUR PART TO KEEP AADAP AFLOAT

Keeping AADAP afloat in turbulent budgetary seas is an "all-hands on deck" effort, and mandates that we pursue potential grant funding opportunities whenever they may arise. As such, we keep a wide-eye out for funding opportunities, and most specifically, we rely on opportunities presented by FDA's Minor Use - Minor Species Grant Program. During the most recent MUMS Grant open period, which closed Jan 15, 2016, we submitted the following four research proposals through Grants.gov:

1. Evaluate the effectiveness of Aquaflor (50% florfenicol) administered at a dosage of 15 mg florfenicol/kg fish body weight/d for 10 d to control mortality associated with BKD in Chinook Salmon;
2. Evaluate the effectiveness of Aqui-S® 20E at a dose of 3 mg/L eugenol when administered as a static bath to lightly sedate rainbow trout for purposes such as grading, sorting, and transporting at low densities;
3. Evaluate the effectiveness of Aqui-S® 20E at a dose of 3 mg/L eugenol when administered as a static bath to lightly sedate Chinook salmon for purposes such as grading, sorting, and transporting at low densities; and
4. 4. Evaluate the effectiveness of Aqui-S® 20E at a dose of 3 mg/L eugenol when administered as a static bath to lightly sedate at low densities cutthroat trout for purposes such as grading, sorting, and transporting at low densities.

We plan to conduct the studies with Chinook Salmon at the Idaho Department of Fish and Game in collaboration with staff at the Eagle Fish Health lab (EFHL). Potential test fish have already been collected and are being reared at the EFHL in anticipation of conducting these studies in 2016. The AQUI-S20E light sedation trials to be conducted on rainbow trout and cutthroat trout will be done at our facilities at the USFWS Bozeman Fish Technology Center. If all are funded, it would mean an additional $146,000 to help support the AADAP program and reimburse the EFHL for expenses they will incur assisting us. We recently heard back from FDA and all grants were awarded! That's not a bad way to start the summer.

Willow Beach NFH visit:

Bonnie Johnson seized upon the opportunity to accompany Dave Miko (Dave Erdahl's boss, and YES there were stories told!) to the Willow Beach NFH during the Aquaculture America 2016 meeting. The hatchery is located 11 miles below the Hoover Dam on the Colorado River and was a welcomed reprieve from the hustle and bustle of Las Vegas. Mark Olson and Tom Frew were able to provide us a tour and show off their razorback suckers. Along with learning about the razorback sucker culture we also learned about the repairs needed for getting the rainbow trout culture up and running again. On our way back to Las Vegas we were treated to a small herd of Desert Bighorn sheep on the side of the road!

Tom Frew, Deputy Project Leader at the Willow Beach National Fish Hatchery (NFH), and Bonnie Johnson, AADAP INAD Coordinator, at the Willow Beach NFH.

	Section:	**Fish Health Management**
	Title:	**Bacterial Coldwater Disease Protocols**
	Original Effective Date:	**June 30, 2010**
	Revised Effective Date:	**November 22, 2010**

Purpose: *Flavobacterium psychrophilum*, the causative bacteria of Bacterial Coldwater Disease (BCWD), has become a major fish health issue not only in Wyoming, but across the western United States. Although mortalities typically range from 5-30% at our facilities, up to 80% losses have been documented in other states.

Rainbow trout brood stocks appear to have the highest infectivity level of BCWD although other species are showing increasing signs. Anecdotally, the bacteria appear to be introduced from the brood stock and are carried by the eggs to the incubator and hatchery.

Fish Culture personnel are proactively working to minimize the bacteria throughout the fish rearing life cycle to reduce BCWD outbreaks. The following protocols were initially developed during a facilitated discussion at the June 2010 Fish Culture Supervisors meeting. Antibiotic treatments are not considered a protocol and are the last resort to combat BCWD.

1. Spawning

a. Use a fresh (first use) water supply to rinse and water harden eggs. Do not use water from the spawning runs or directly from any rearing units.

b. Green eggs from captive brood stocks shall be treated after water hardening with iodine (100 ppm for 10 minutes) prior to shipment, then rinsed and shipped in fresh water. If the brood facility is the receiving incubator, this step is not required since they will be treated twice on site before incubation.

2. Incubator

a. Green eggs shall be treated twice with iodine, 100 ppm for 10 minutes, before placing in the incubator, rinsing with fresh (first use) water between treatments.

b. If practical, treat incubating and eyed eggs with alternating treatments of formalin (1,000 ppm – 2,000 ppm for 15 minutes) and hydrogen peroxide (500-1,000 ppm for 15 minutes. Formalin is not effective in reducing *Flavobacterium psychrophilum*.

c. Eyed eggs shall be treated five (5) straight days with hydrogen peroxide (500-1,000 ppm for 15 minutes) prior to shipment to reduce the bacterial load as much as possible.

d. Eyed eggs shall be treated twice with iodine (100 ppm for 10 minutes) and rinsed with fresh (first use) water between treatments before measuring into the hatchery rearing units; even if the incubating station is the receiving hatchery.

3. Proactive Fish Rearing

a. Salt Treatment (two treatments are preferable).

i. If initial signs of BCWD are noted with sac-fry, treat with a salt bath at 0.5 to 1.0%. (cutthroat and grayling, consider lower concentration).

ii. For small feeding fish, treat with a salt bath up to 2.0%.

b. Feed – all feed to size #3 will be supplemented with probiotics at the feed mill.

c. To reduce any bacterial loading in a rearing unit or downstream rearing, remove dead and moribund fish promptly, especially if the lot in question is assumed to be infected with BCWD.

d. If practical, thinning a lot may be beneficial if an infection is detected early. However, a thinned lot does not always prevent BCWD, but may reduce the severity of an infection.

4. Proactive Fish Distribution

a. Salt Treatment for fish transfers between stations.

b. Receiving station sets up treatments, 0.5% initially, increasing the total concentration to 1.5 to 2.5% in transit or upon arrival (20 minutes to 1 hour based on fish behavior). Exact treatment time and salt concentration depends on the experience noted with various species at each station.

c. If the fish are showing signs of BCWD, consider treating fish transfers with hydrogen peroxide, either in the distribution tank at arrival or receiving rearing unit. Care must be taken if this treatment is considered.

5. Bio-Security

a. Hand sanitizers shall be used between rearing areas (e.g. incubator to hatchery, hatchery to outside rearing units) and utilized between handling each lot. It is not feasible to employ hand sanitizers for outside rearing units or unheated buildings.

b. Virkon foot baths are to be placed in hatchery entries and doorways for incubators and isolation facilities.

c. It is recommended all equipment shall be disinfected with Virkon between uses, especially between lots (use weed sprayer and small buckets for dipping). It is preferable to have separate brushes etc. for each lot if disinfection is not feasible in outdoor environments. If an infection is noticed in one rearing unit of a lot, equipment shall be either isolated to that unit or disinfected before using in remaining lot rearing units.

d. Incubators, jars, baskets and rearing units shall be emptied, cleaned with an approved cleaning compound, and air dried when possible. Each unit shall be disinfected with Virkon before repopulating.

e. Distribution tanks shall rinsed and disinfected with Virkon (spray on application) or chlorine (under standard disinfection protocols) prior to using for transfers between stations. Chorine disinfection is still the standard protocol for out-of-state trip procedures.

Halamid® Aqua (Chloramine-T) Approved by FDA to Treat Fish Disease – What It Means for Fisheries

Jesse T. Trushenski, Southern Illinois University Center for Fisheries, Aquaculture, and Aquatic Sciences, Carbondale, IL, saluski@siu.edu

James D. Bowker, U.S. Fish and Wildlife Service Aquatic Animal Drug Approval Partnership Program, Bozeman, MT, jim_bowker@fws.gov

Axcentive SARL announced recently that the U.S. Food and Drug Administration (FDA) has approved Halamid® Aqua (100% chloramine-T) as a new therapeutic drug for use in fish. Halamid® Aqua is an important weapon in the arsenal fisheries professionals use to combat fish diseases, and its approval is a major advance in fish health management. Below, Jesse Trushenski, President of the Fish Culture Section, discusses the approval with Western Division Vice-President, Jim Bowker, who has played a leadership role in fish drug approval efforts for the past 20 years.

What is chloramine-T and what is it used for?

Chloramine-T is a chlorine-releasing product that's used as a sanitizing agent in hospitals, other medical and dental facilities, laboratories, and veterinary facilities. Chloramine-T kills microbes through non-selective, oxidative processes. In other words, it's a disinfectant and not an antibiotic. Chloramine-T kills Gram-negative bacteria, including the fish pathogens associated with bacterial gill disease (BGD) and columnaris. After more than 20 years in development, Halamid® Aqua (100% chloramine-T) has been approved by the FDA to control mortality in freshwater-reared salmonids caused by BGD and in walleye and freshwater-reared warmwater finfish caused by columnaris.

This seems like very good news for fish culture and fish health types, but why does it matter to 'Joe Fish Biologist'?

Whether it's for creating new fishing opportunities or restoring imperiled species, fish culture and hatchery-reared fish are central to fisheries management. Many fish pathogens are ubiquitous and, like all of us, when crowded together like fish are in intensively reared systems, they become more susceptible to infections. When disease outbreaks occur, it's essential that we have a well-stocked medicine chest to treat the infections, ensure production goals are met, and fish are healthy when they are released into our waters. Stocking healthy fish should not only matter to Joe Fish Biologist, but to anglers and all those interested in fisheries conservation.

Billions of fish are stocked in the U.S. annually, mostly for sportfishing, but also for restoration and recovery of threatened and endangered fish. FDA-approved fish drugs, like Halamid Aqua, help culturists safely and effectively control mortality in the hatchery. That means time and money are not wasted on rearing fish that succumb to disease. We all know resources are limited in fisheries conservation; Halamid Aqua isn't a silver bullet, but judicious use of chloramine-T and other approved drugs can help hatcheries operate more effectively.

20+ years seems like a long time for a drug to be in development. What did it take to secure this approval?

That's a question that has been asked for…well, about 20 years! Approval of a chloramine-T product has been the #1 priority of the Association of Fish and Wildlife Agencies (AFWA) Drug Approval Working Group since its inception, and it has been a long road. FDA takes a precautionary approach to drug approvals and proving a drug is safe and effective requires volumes of data generated under strict regulatory oversight. Chloramine-T was the first AFWA drug priority we tackled collectively, and we charted new territory in the process. Without the commitment of the sponsor, several research entities, and the National New Animal Drug Application Coordinator, Halamid Aqua would never have been approved.

What have you learned during the development of chloramine-T? Will the process always be this laborious?

We learned from our mistakes. We now communicate more frequently with FDA, and we have learned to ask the right questions. We've become experts in the drug approval process and have developed expertise in the related fisheries disciplines, and that has made the process much less laborious and lengthy. For example, we're currently working towards an approval for an immediate-release fish sedative, and we anticipate this drug will be approved in less than half the time it took for Halamid Aqua.

Does this mean the fisheries medicine chest is now full?

Unfortunately, no. Several more fish drugs are still critically needed, including another antibiotic to better address issues such as antimicrobial resistance. We've got a handful of options for freshwater fish, but the medicine chest for marine fish is empty.

Congratulations and thanks are due to all those who have contributed to this approval over the years. What can fisheries professionals do to express our gratitude for those who toil in the field of aquatic animal drug approvals?

Thank you. First, it is critical that fisheries professionals use only FDA-approved drugs and that they use them judiciously. Second, make a commitment to help groups like the U. S. Fish and Wildlife Service Aquatic Animal Drug Approval Partnership Program to conduct field effectiveness trials. If you don't help prove a drug is effective in your fish, it's unlikely that it will be approved for that use. Opportunities to conduct scientifically valid, statistically defensible, field effectiveness trials are the biggest limiting factor in getting drugs approved for new uses. Halamid Aqua is now approved for a few uses, but by helping us conduct the necessary experiments, you can help expand the label enabling use by more fisheries professionals in need.

UMESC Corner

Eugenol

UMESC completed work to characterize the depletion of eugenol (the marker residue for AQUI-S® 20E) from rainbow trout (*Onchorynchus mykiss*). The study was conducted to fulfill a portion of the drug depletion component of the human food safety requirements for AQUI-S® 20E. Rainbow trout were exposed to AQUI-S® 20E in water at a temperature of 9°C, a temperature that is representative of the lower range of temperatures where rainbow trout would be sedated. Eighty fish were exposed to a nominal AQUI-S® 20E concentration of 100 mg/L for 60 min. Groups of 16 fish were sampled after 60 min of exposure (the 0 h sample group), then at 15, 30, 90, and 150 min after transferring the fish to flowing freshwater. Skin-on fillets from each fish were analyzed for eugenol concentrations using a U.S. Food and Drug Administration Center for Veterinary Medicine (CVM) approved method for determining eugenol concentrations in fish fillet tissue, a method developed and validated at UMESC. The comprehensive final report describing the results of the study was submitted to CVM. Contact Jeff Meinertz, jmeinertz@usgs.gov, for more information.

UMESC conducted studies to assess the mortality of fish hauled for 6 h in transport tanks containing AQUI-S® 20E. There were 3 treatment groups for each of 2 species tested, Nile tilapia (*Oreochromis niloticus*) and yellow perch. Treatment groups were (1) non-treated control, (2) 100 mg/L AQUI-S® 20E, and (3) 200 mg/L AQUI-S® 20E. The loading density in the transport tanks for tilapia was 480 g/L and 240 g/L for yellow perch. Target AQUI-S® 20E concentrations in transport tanks were verified before fish were transferred to transport tanks. During transport, water samples were taken from transport tanks for analyses to determine AQUI-S® 20E concentrations through the transport period. Temperature, 22°C (±2°C) for tilapia and 17°C (±2°C) for yellow perch was regulated through the transport period. After the transport period, fish were returned to flow through holding tanks and monitored for 14 days. Summarization and interpretation of the data are ongoing. Contact Theresa Schreier, tschreier@usgs.gov, for more information.

Formalin and Hydrogen peroxide

UMESC conducted literature reviews to summarize available data regarding the impact of formalin and hydrogen peroxide on the biology of recirculating aquaculture system (RAS) biofilters were published as USGS Open File Reports. UMESC conducted studies to determine the effects of Parasite-S and 35% Peroxaid® on RAS biofilters. The studies are being conducted to provide data to CVM for potential label expansion of Parasite-S and 35% Peroxaid® allowing for their use in RASs. Preliminary studies to determine the concentration of each product that is potentially safe for production sized biofilters have been completed. Field trials assessing the impact of the potentially safe Parasite-S concentrations on biofilters of 2 sizes of RASs have been completed. Summarization and interpretation of the data from those studies are ongoing. Similar field trials are planned for 35% Peroxaid®. Contact Kim Fredircks, kfredricks@usgs.gov for more information.

CVM Corner

Greetings! There are a number of important updates from FDA to share with you. While I've provided a number of web links in the text below, if you have additional questions for FDA's Center for Veterinary Medicine, please submit your questions to AskCVM@fda.hhs.gov.

Certain drugs for fish will require veterinary oversight beginning January 1, 2017

Several of the drugs approved to treat fish that are currently available over-the-counter will require a Veterinary Feed Directive (VFD) order or veterinarian's prescription starting January 1, 2017. The specific drugs affected are the antimicrobials that are of medical importance to humans and are fed to food producing animals via feed or water. These drugs include oxytetraycline and sulfadimethoxine/ormetoprim products that are administered in feed or water to fish. The drug companies with approved products have indicated that they will voluntarily participate in an effort initiated by FDA to make sure medically important antimicrobials administered to food producing animals come under veterinary supervision and are not used for weight gain or feed efficiency purposes and that they will adjust the labeling of their products accordingly by the end of 2016.

This effort aligns with FDA policy which is part of a national strategy to address antimicrobial resistance. It is important that people who may need to treat fish with these drugs understand in advance how these changes will impact them in January 2017; we strongly encourage you to reach out to a veterinarian before these changes go into effect so you are not trying to figure things out for the first time when a disease outbreak occurs.

It is also important to note that FDA updated the VFD regulations in June 2015, with the new regulations becoming effective October 1, 2015. Veterinarians, feed mills, and clients should be aware of these new regulations, as they currently apply to the VFDs written for Aquaflor and will apply to VFDs needed for any other drugs that will be approved as VFD drugs. Additional information can be found on CVM's webpage for Veterinary Feed Directive Drugs.

FDA takes several actions involving genetically engineered plants and animals for food

In November 2015, FDA issued the first approval for a genetically engineered (GE) animal intended for food and published two guidances for manufacturers who wish to voluntarily label their products as containing ingredients from GE or non-GE sources.

The FDA approved AquaBounty Technologies' application for AquAdvantage Salmon, an Atlantic salmon that reaches market size more quickly than non-GE farm-raised Atlantic salmon. The FDA regulates GE animals under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act, because the recombinant DNA (rDNA) construct introduced into the animal meets the definition of a drug. In this case, the rDNA construct introduces a trait that makes the AquAdvantage Salmon grow faster. Information regarding the approval can be found on FDA's website.

The Fiscal Year (FY) 2016 Omnibus Appropriations Act covering the funding of the federal government during fiscal year 2016 (FY16) was signed into law by the President on December 18, 2015 becoming Public Law No: 114-113. In part, this law directs that during FY16 the FDA shall not allow the introduction or delivery for introduction into interstate commerce of any food that contains genetically engineered salmon, until FDA publishes final labeling guidelines for informing consumers of such content.

Changes in FDA leadership

The FDA recently announced several changes in leadership. In February 2016, Dr. Robert Califf was appointed FDA Commissioner. There will also be a change of FDA's Deputy Commissioner for Foods and Veterinary Medicine as Michael Taylor announced that he will be leaving on June 1, 2016. Dr. Stephen Ostroff, who was the acting FDA Commissioner until Dr. Califf's appointment, will become the next Deputy

Commissioner for Foods and Veterinary Medicine. Additionally, Dr. Bernadette Dunham, the Director of FDA's Center for Veterinary Medicine (CVM), recently announced that she will be leaving the agency in April to participate in a One Health collaborative effort between the Milken Institute School of Public Health at the George Washington University and the FDA. Tracey Forfa, J.D., who has served as CVM Deputy Director since 2008, will be the Acting Center Director beginning April 4, 2016, while the agency conducts a nationwide search for a new director for CVM.

ARS Corner

Aquaculture America 2016

The Aquaculture Drug Research and Drug Approval Status special session is taking a hiatus this year and may come back in the future. Jim Bowker and Dave Straus have been very successful with this session for the past13 years and it was time for us to take a rest. Maybe there are some new researchers that would like to work on this???

Copper Sulfate

As most of you know, copper sulfate **is not** approved by the FDA as a drug in aquaculture; however, regulatory action is deferred while we are working toward gaining approval of it to control Ich on channel catfish and saprolegniasis (fungus) on channel catfish eggs. Therefore, its use as a drug is currently acceptable.

We finally submitted the manuscript on using copper sulfate to control fungus in a sunshine bass hatchery, and it was recently accepted by the North American Journal of Aquaculture. This will be the second paper on its effectiveness at controlling fungus on eggs (channel catfish eggs was the other paper); we also have research to publish on effectiveness with largemouth bass eggs and we are currently researching use on rainbow trout eggs. The idea is that once copper sulfate is approved, it will be Over-the-Counter (OTC), but we want research to be there for veterinarians to justify extra-label use.

Typical fungus in a sunshine bass hatchery.

Healthy and fungus-covered CCF eggs at USDA-ARA SNARC, AR.

Hatching experiment in a sunshine bass hatchery.

Now, more about our drug-approval efforts.

Our previous Sponsor, Freeport-McMoRan, sent a letter to their customers in July 2015 that they had decided to stop producing CuSO4. We immediately began efforts to find a new Sponsor. By October, we had Chem One Ltd. agree to partner with us, and they became the official copper sulfate Sponsor with a letter from FDA/CVM in December.

Since we now have a new Sponsor, they have requested a presubmission conference with FDA/CVM to discuss the procedures for approval of their product and work on any remaining items to be accomplished, especially the **Chemistry, Manufacturing and Control (CMC)** Technical Section, which is the last major technical section required for the Ich label (see below).

We have two designations, or labels, we are striving for with copper sulfate:

1) For the treatment of ichthyophthiriasis (*Ichthyophthirius multifiliis*) on channel catfish cultured in earthen ponds.

All major Technical Sections for this label (besides **CMC**) are Complete except for **Environmental Impact** for earthen ponds. The Environmental Assessment (EA) for this indication was submitted in 2014 and revised according to FDA comments in 2015. A letter from FDA/CVM was received just before Christmas that accepted the EA in support of a finding of no significant impact (FONSI). A letter was sent to FDA/CVM by the sponsor requesting an **Environmental Impact** Technical Section complete letter, and we await the their response. The **Labeling** and **All Other Information** Technical Sections will be submitted pending the status of the **Environmental Impact** and **CMC** Technical Sections.

2) For the control of mortality in channel catfish eggs due to saprolegniasis (fungi of the family Saprolegniaceae).

All major Technical Sections for this label (besides CMC) are Complete except for **Environmental Impact** under a hatchery scenario. A consulting firm is preparing a proposal for the EA and we hope to get started soon. Again, the **Labeling** and **All Other Information** Technical Sections will be submitted pending the status of the **Environmental Impact** and **CMC** Technical Sections.

Dave Straus, USDA/ARS, Harry K. Dupree – Stuttgart National Aquaculture Research Center, Stuttgart, AR.

Fish Farming News
Aquaculture's National Newspaper - Volume 22 - Issue 5 - 2015 - A Compass Publication

Why INADs are a fish farmer's best friend

FISH HEALTH NOTES
BY ROD GETCHELL

BOZEMAN, MT – Fish farmers can use Investigational New Animal Drug (INAD) exemptions to medicate their fish with certain drugs that have not yet been approved for use, as long as they follow useguidelines and collect data that can contribute to the eventual approval of the drug.

At this year's Aquatic Animal Drug Approval Partnership (AADAP) meeting, which was held July 27-30, INAD Coordinator Bonnie Johnson summarized 15 years worth of INAD data collection.

I was so impressed with the number of aquaculturists who had contributed to the program and with the number of fish lives saved that I had to put the information in front of you.

The AADAP office at the US Fish and Wildlife Service's Bozeman Fish Technology Center is somewhat understaffed these days, at least compared to previous years, so the current crew has had to scramble a bit keeping up with all the data that fish farmers are contributing.

But Bonnie still was able to present some amazing statistics.

From 1999 to 2014, roughly 1.3 billion fish were treated with various drugs under INAD exemptions. It's an incredible figure when you try to visualize that many animals.

Five hundred seventy-one federal, state, private, tribal, and university facilities participated in the effort, all generating muchneeded data to be compiled for the potential approval of new disease treatment options.

The reason this program is so important is because fish are considered a "minor species" in the drug world, and very few "approved" drugs are on the market right now to treat minor species.

This situation has seriously hampered the aquaculture industry in the past, which is why being able to treat fish under an INAD exemption has been a welcome step forward.

Clearly, fish farmers and hatchery personnel are willing to do the required data collection, hoping the information will help lead to more drugs being approved and readily available in the future.

If a pharmaceutical company had to pay for this kind of research, new options for disease treatments would never move forward in the long approval process.

Bonnie graciously let me use some of her slides to show you the breakdown of the fish species most studied through the National INAD Program and where the work was completed (see figures).

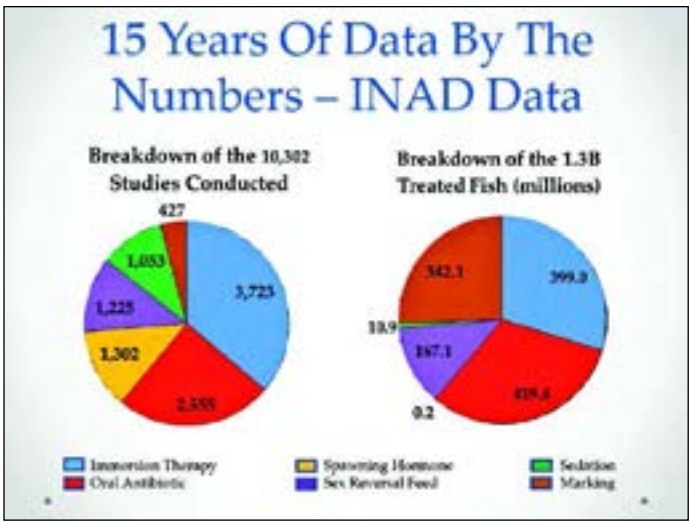
History

The National INAD Program was started in 1998.

Contributors and users include all US aquaculture facilities, field biologists, and researchers.

As funding to AADAP has been cut, INAD participant costs have had to be recovered through user fees.

The AADAP folks at US Fish and Wildlife work with US Food and Drug Administration (FDA) professionals and drug sponsors from the pharmaceutical industry who ultimately must get these new therapeutants licensed.



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The types of studies conducted under the INAD exemptions have included immersion therapies, oral antibiotics, spawning hormones, sex reversal treatment, sedation, and marking for later age and/or survival determination.

The life stage of fish studied follows the trend you would expect. Younger, more susceptible but easier-to-treat fry and fingerlings are more frequently dosed under INAD exemptions.

The data collected at fish hatcheries throughout the country, under real life situations, provides invaluable information for regulators who must determine whether the suggested new compounds are indeed effective in the manner in which they are used.

Bonnie Johnson wearing the AADAP bag.

Important data on the safety of the chemicals or therapeutics also is collected.

Drugs are not approved until proven safe.

Regulatory authorities take a precautionary approach to any substances that may enter the environment or be consumed by people or have an adverse effect on fish being raised for food.

Fish folks are just as careful in protecting the health of the fish they raise.

The American Fisheries Society (AFS) recently pointed out that the most common water treatments applied in hatcheries are low doses of hydrogen peroxide, which breaks down to carbon dioxide and water, and chloramine, a common disinfectant.

AFS also makes the case that hatchery effluents are minor compared to the pharmaceutical and personal care products that enter our country's waterways.

Why are INADS important?

Without the assistance of all these users and the effort that AADAP expends to collate and organize this data, most drug sponsors could not afford to conduct these required safety and effectiveness studies.

It comes down to the bottom line really.

If a drug company cannot recover its research and development costs when it puts a product on the market, the company simply will not expend the effort in the first place.

Inequities in drug availability represent serious management and economic problems for producers of minor animal species like fish.

These drug trials show researchers and FDA what does and doesn't work in specific fish species that run into trouble at our local fish farms or agency hatcheries.

The "One Health" folks here at the Cornell veterinary college where I work believe the health of humans is connected to the health of animals and the environment.

The science behind animal health and human health is really no different.

Whatever our mission is, we need to monitor and control health threats.

Our own medical doctors collect the same kind of information as those of you who go through the trouble to collect data to send to Bonnie in Bozeman.

INADs are a lifesaver for the small farmer and the large establishment.

Learn more

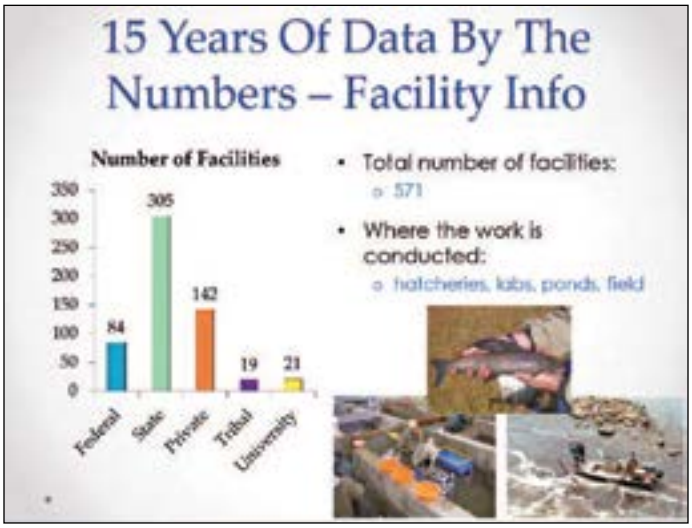
The AADAP website can be found at <https://www.fws.gov/fisheries/aadap/home.htm>. It contains much more information about INADs, the National INAD Program, and general drug use guidance.

However, the website does need a bit of updating. So if you see or hear conflicting information about the program, don't hesitate to contact Bonnie Johnson herself for clarification. She can be reached by e-mail at <bonnie_johnson@fws.gov>.

One thing I am not conflicted about is the dedication of the AADAP staff in Bozeman.

They contribute much to the health of US fish stocks and should be lauded for their largely unheralded efforts.

Dr. Rod Getchell works in the Aquatic Animal Health Program at the Cornell University College of Veterinary Medicine.



Publications

1. Jennifer L. Johnson, Jesse T. Trushenski & James D. Bowker. 2016. Induction, Recovery, and Hematological Responses of Pallid Sturgeon to Chemical and Electrical Sedation, North American Journal of Fisheries Management, 36:3, 568-575, DOI: 10.1080/02755947.2016.1141121

2. Bowker, J. D., D. G. Carty, J. T. Trushenski, D. C. Glover, and M. P. Bowman. 2015. Considerations for Consistently Applying Flow-through Chloramine-T Treatments to Hatchery Raceways. North American Journal of Aquaculture 77:524-531.

3. Bowker, J. D. 2015. Mythbusters: What's real and what's not when it comes to fish drugs. North American Journal of Aquaculture 77:358-366.