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

Volume 4-2

AADAP NEWSLETTER

July 2008

WHAT'S SHAKIN'

Hot off the presses...new oxytetracycline (Terramycin® 200 for Fish) supplemental approval for Phibro Animal Health: Phibro Animal Health today (9 July 2008) received official confirmation from FDA's Center for Veterinary Medicine that Phibro's Supplemental New Animal Drug Application for oxytetracycline medicated feed product has been approved for the additional claims of: 1) coldwater disease in all freshwater reared salmonids, 2) columnaris in all freshwater reared *Oncorhynchus mykiss,* 3) marking of Pacific salmon and 4) treatment of salmonids for approved diseases at all temperatures (i.e., removal of prohibition of treatments below 9°C). Congratulations to Phibro, CVM and all others involved in bringing this to fruition. For more information on activities regarding this supplemental approval refer to Roz's Corner.

AQUI-S® use on food fish under INAD 10-541 strictly prohibited: Use of AQUI-S® for food fish is now strictly prohibited under U.S. Fish & Wildlife Service's INAD 10-541. Isoeugenol (the active ingredient in AQUI-S®) has recently been evaluated by the National Toxicology Program (NTP), an interagency program whose mission is to evaluate chemical agents for potential public health risks. The NTP has concluded that the exposure of male mice to isoeugenol resulted in clear evidence of cancer. As a result of these findings, the U.S. Food and Drug Administration's Center for Veterinary Medicine (CVM) has officially rescinded authorization for the "investigational food use" of AQUI-S® under INAD 10-541. Use of AQUI-S® on nonfood fish under INAD 10-541 will not be prohibited, but will be granted only on a case-by-case basis. Please contact Dave Erdahl (phone: 406-994-9904; email dave_erdahl@fws.gov) with questions or comments.

14th Annual Aquaculture Drug Approval Coordination Workshop reminder: The 14th Annual Workshop will take place in Bozeman, Montana on the Tuesday, Wednesday and Thursday (29-31 July 2008) immediately before Bozeman's Sweet Pea Festival (1-3 August 2008). Please check AADAP's Workshop-webpage for the latest details on the Workshop, *per se*, as well as accommodations, etc. If you are planning on attending, please make your hotel reservations as early as possible. Due to the Sweet Pea Festival hotel rooms are at a premium during this period.

Announcements for meetings associated with 2008 Aquaculture Drug Approval Coordination Workshop now online: Four separate meetings are being held this year in association with the 14th Annual Aquaculture Drug Approval Coordination Workshop. On Monday morning, 28 July, there will be a round-table discussion session focusing on ectoparasite efficacy study conduct, and the dilemma of reinfection or reinfestation that may occur during the posttreatment data collection period. On Monday afternoon there will be a short coordination meeting of researchers and regulators involved in the approval process for 17α-methyltestosterone. On Friday morning, 1 August, the National Aquaculture Drug Research Forum will meet and in the afternoon there will an organizational meeting of the newly formed group, the National Aquaculture Industry - Therapeutic Agents Program (NAI-TAP). The NAI-TAP is being created to assume many the functions of the soon-to-dissolve Joint Subcommittee on Aquaculture's Working Group on Aquaculture Drugs, Biologics and Pesticides. The above described meetings are open to anyone interested in attending. For detailed information on these associated meetings, go to: http://www.fws.gov/fisheries/aadap/inadworkshop08.htm or click here.

15th Annual Aquaculture Drug Approval Coordination Workshop planned for Little Rock, Arkansas: The planning and preparations for the 15th Annual Workshop are ongoing and progressing well. The Workshop will be co-hosted by USDA's Stuttgart National Aquaculture Research Center (SNARC) and USFWS's Aquatic Animal Drug

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Approval Partnership (AADAP) Program. The folks at SNARC have set the dates for the Workshop; Tuesday 9 June through Thursday 11 June 2009. Tentatively, both Monday 8 June and Friday 12 June are dates being set aside for associated meetings and extracurricular activities. As more details become available, they will be posted on AADAP's website on the 2009 Workshop webpage.

New zero-withdrawal anesthetic candidate being sought: Given the recent news regarding the determination by the National Toxicology Program that clear evidence of cancer induction has been demonstrated for isoeugenol (the active ingredient in AQUI-S®), the aquaculture community is now searching for a new candidate zero-withdrawal anesthetic. These search efforts are being lead by members of the Association of Fish and Wildlife Agencies' Drug Approval Working Group (DAWG). A new candidate drug has not yet been identified, but several drugs are being considered, including eugenol, metomidate, benzocaine and tricaine methanesulfonate. As new information becomes available, it will be posted on AADAP's website. For a historical perspective of the DAWG and its members' activities on AQUI-S® and other zero-withdrawal anesthetics refer to the Feature Article in this edition.

Florida's Richloam Hatchery receives recognition for outstanding performance: The Association of Fish & Wildlife Agencies (AFWA) recently sent a letter to the Executive Director of the Florida Fish and Wildlife Conservation Commission commending his staff for "steppin' up to the plate" by conducting several pivotal efficacy studies on cool and warmwater fish. In particular, Mr. Michael Matthews and his colleagues at the Richloam Fish Hatchery (Florida Bass Conservation Center) were recognized for their exemplary contributions. A copy of the letter sent to the State of Florida, along with other AFWA documents and products, can be viewed on AFWA's page of AADAP's website (http://www.fws.gov/fisheries/aadap/afwa-dawg.htm).

Speaking of Richloam Fish Hatchery: Thanks once again to Michael Matthews, Josh Sakmar and Justin Elkins of the Florida Bass Conservation Commission's Richloam FH for all their hard work in conducting pivotal efficacy studies. This past spring Richloam FH completed not one, but two additional pivotal efficacy studies! The first study evaluated chloramine-T treatment (20 mg/L on 3 alternate days) to control mortality caused by external columnaris in bluegill. The second study evaluated Aquaflor® treatment (fed at a rate of 10 mg/kg fish weight for 10 consecutive days) to control mortality caused by systemic columnaris in largemouth bass. Although CVM will of course have the final say on treatment effectiveness following submission of final study reports, preliminary results appear promising as in both studies cumulative percent mortality in control test tanks was higher than in treated test tanks. Thanks for your continuing hard work guys!

More good news from Florida: Thanks to Roy Yanong and his staff at the University of Florida's Tropical Aquaculture Laboratory for helping out with fish health sampling during the recent Aquaflor® pivotal efficacy study conducted at Richloam FH. We know it's a long drive from Ruskin, Florida to Webster, Florida - but not nearly as long as the trip from Bozeman, Montana to Webster! Thanks for stepping up to help us out!

Welcome aboard! Kelly Winningham of the Arkansas Game and Fish Commission's Andrew Hulsey Fish Hatchery, and Martha Wolgamood and Matt Hughes of the Michigan Department of Natural Resource's Wolf Lake State Fish Hatchery have recently (and willingly!) entered into the pivotal efficacy study do-loop. Kelly is planning to start a 35% PEROX-AID® study on largemouth bass infected with external columnaris in the next couple of weeks, while the folks at Wolf Lake SFH plan to start a 35% PEROX-AID® study on muskellunge infected with external columnaris early this summer. Good luck to all, and thanks much for stepping up to the plate!

Designation of cold, cool, and warmwater fish species proposed to CVM: On 24 October 2007, AADAP, in coordination with the National Aquaculture Drug Research Forum, submitted a proposed temperature-based species classification system to CVM. The proposed system was developed utilizing information collected on approximately 100 fish species reported in the 2005 Public Aquaculture Production Database (available on AADAP's website; click here to access); *the most common rearing water temperature range for each species* was used as the basis for establishing categories. The proposed system groups U.S. publically cultured finfish into one of four rearing temperature categories: (1) coldwater fish, those species reared at water temperatures < 12°C; (2) coolwater fish, species reared at temperatures between 12-18°C; (3) warmwater fish, species reared at temperatures > 18°C; or (4) coolwater/warmwater "crossover fish" that are reared at temperatures > 12°C

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(i.e., fish commonly reared in either cool **or** warmwater). This classification system is intended to provide guidance (to both CVMers and aquaculturists) when determining if the use of an approved drug on a specific fish species is in accordance with on-label or off-label use (e.g., 35% PEROX-AID® approved for use in all freshwater, *coolwater* finfish), and also when developing data requirements for future drug approvals. Click here to view the complete proposed temperature classification system, including a more detailed description of categories and respective justifications. Stay tuned to learn what CVM's opinion will be!

Aqui-S® update:

AQUI-S® as a zero-withdrawal anesthetic: What happened on the way to a New Animal Drug Application: see the Feature Article in this edition of the Newsletter.

Copper sulfate (Triangle Brand Copper Sulfate®) update:

Refer to USDA's Corner.

Halamid® (chloramine-T) update:

Largemouth bass/external columnaris efficacy study accepted as pivotal: Great news! AADAP received word from CVM on 14 April 2008 that one of the chloramine-T studies conducted at Richloam Fish Hatchery (Florida) had been accepted as pivotal. The study was conducted to evaluate the effectiveness of 20 mg/L chloramine-T administered in a daily static bath for 60 min on three consecutive days to control mortality in largemouth bass caused by external columnaris associated with *Flavobacterium columnare*. In this study, mean cumulative mortality at the end of the 14-day posttreatment period was significantly ($p = 0.010$) lower in treated tanks (27%) than in control tanks (35%). Mucho thanks to the Richloam gang for their efforts, and to Mark Gaikowski (USGS/UMESC) for his assistance with data analysis.

Unfortunately, CVM review of a second field study conducted at Richloam Fish Hatchery to substantiate the effectiveness (as demonstrated in the study noted above) of chloramine-T to control mortality in largemouth bass caused by external columnaris was not as positive. AADAP received a letter from CVM on 23 May 2008 informing us that the study was not accepted. However, following a conference call with CVM's Aquaculture and Biometrics Teams to discuss CVM concerns with respect to the final study report (FSR), it appears that resubmission of a revised FSR may result in study acceptance. Of primary concern was a request by CVM that we reanalyze cumulative mortality data and adjust the number of fish at risk midway through the study in one of the test tanks.

For more information on chloramine-T see Roz's Corner.

Oxytetracycline (OTC) update:

Administrative NADA submitted: On 2 June 2008 Phibro Animal Health submitted an administrative NADA to CVM for the supplemental claims: 1) columnaris disease in freshwater-reared *Oncorhynchus mykiss* and (2) coldwater disease in all freshwater-reared salmonids. Additionally, the current claim of treatment only above 9°C will be removed, effectively allowing for treatment at any temperature.

See front page for CVM's notice of approval.

For more information on OTC see Roz's Corner.

Text provided by Paul Duquette; Phibro Animal Health, Ridgefield Park, New Jersey, USA.

Potassium permanganate update:

Refer to USDA's Corner.

17α-methyltestosterone (17MT) updates:

Effectiveness Final Study Report Resubmitted: In support of a new animal drug application (NADA) for use of 17 α-methyltestosterone to produce predominantly male populations of tilapia, AADAP resubmitted to CVM a data package comprising: 1) revised "Final Study Reports" for three field effectiveness studies conducted in 2006 and 2007; (2) a revised "Multi-Site Data Analysis Report", and (3) a "Report to Justify Reclassifying 17 α-Methyltestosterone Efficacy Treatment Successes". This data package weighed a meager 60 lbs (!!!) and was resubmitted to CVM on 13 June 2008. The impetus for the resubmission was comments made by the Aquaculture Team in a letter to us dated 1 May 2008. We worked closely with Dr. Susan Story (CVM Aquaculture Team) and Dr. Todd Blessinger (CVM Biometrics Team) to address the comments, and we thank them for their patience and help. Once we figured out what we needed to do, virtually the entire AADAP staff worked on the revisions and prepared the data package for submission. Now we're back in the wait-and-see mode, and waiting patiently to find out if the effectiveness technical section will be considered complete for this claim. Stay tuned.

For more information on 17MT see Roz's Corner.

35% PEROX-AID® (hydrogen peroxide) update:

Research study protocol accepted first time around: First time ever! On 21 April 2008, AADAP submitted to CVM a research study

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protocol entitled: "The efficacy of 35% PEROX-AID® (35% hydrogen peroxide) to control mortality due to saprolegniasis in freshwater-reared finfish." On 6 June 2008, AADAP received a protocol concurrence letter from CVM; no revision required!

FINS & TAILS, BITS & BOBBERS

American Fisheries Society (AFS) and AADAP to publish an aquaculture drug use poster: The AFS's Fish Culture (FCS) and Fish Health Sections (FHS) have partnered with the AADAP program to produce a Quick Reference Guide poster titled "Approved Drugs for Use in Aquaculture." The poster is intended to serve as a useful outreach product that will hopefully minimize some of the confusion that typically arises regarding what approved drugs are available to fisheries biologists, as well as how and when they may be used.

The poster is currently being made available to all FCS and FHS members. It is also being made available to non-FCS/FHS folks on a first-come/first-served basis. Anyone who is interested in receiving a copy of the poster should contact Jim Bowker at 406-994-9910 or jim_bowker@fws.gov. Supply is limited so don't delay! The poster is constructed of a laminated heavy-weight paper and designed to be used in, or in close proximity to, fish-rearing environments.

Automation of INAD reporting being planned: AADAP has begun the process of moving our INAD reporting procedures into the Web-age. Currently, each of the 200+ co-investigators working under INADs held by the U.S. Fish & Wildlife Service (FWS) are responsible for submitting (in hard-copy paper form) 4-6 forms for each treatment event…for each INAD in which they are enrolled. AADAP in turn, as required by FDA's Center for Veterinary Medicine (CVM), must compile the information contained on these forms, and then summarize and report this information to CVM.

To facilitate these activities, all the collected information is currently hand-entered into an AADAP-designed database. Inherently, the transcription of information from paper forms to a computer database is extremely labor-intensive. This process also has the inherent potential for transcription errors.

AADAP is currently in the early stages of developing a web-based system for INAD reporting. As envisioned, when the new system is up-and-running, co-investigators under FWS INADs will no longer need to fill out paper forms, but will complete the required "paper-work" totally on-line. As planned, the system will additionally remind (via email) co-investigators of their obligations (i.e., reporting requirements) and will contain built-in features to eliminate co-investigator entry errors.

Given the regulatory hurdles to accomplish this change-over, not to mention the development and testing *per se* of the user interface and web database, implementation of the new INAD reporting system will probably not occur until 2009. So those FWS INAD co-investigators with a web-phobia have probably a year or so to prepare. Stay tuned; we'll keep you informed as we progress, and may even call on a few of you to "test-drive" a prototype version.

National INAD Program (NIP) update: The NIP continues to be an extremely successful program for

Map of the United States Showing Federal, State, Tribal, and Private Aquaculture Participation (by Number of Facilities) in the National INAD Program Calendar Year 2008

the USFWS and partner facilities/agencies. To date in FY 08 there are over 200 federal, state, private, and tribal facilities participating in 43 different states and one U.S. territory. Currently 13 different INADs are available for use, with several additional INADs "in the works."

Calendar Year 2007 NIP study submission statistics: NIP participants - please do not feel like the "Lone Ranger" out there when you are filling out your required INAD paperwork. Last year was another 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 2007 studies:

1. Number of completed study reports submitted to the AADAP Office – 700
2. Number of reporting facilities - 136
3. Number of INADs used - 12
4. Number of treated fish – 72.7 million fish
5. Species of fish treated – 18 salmonid species; 29 non-salmonid species; 7 marine species; 1 aquarium species; and 2 shellfish species
6. Number of Quarterly Reports submitted to FDA/CVM – 52

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7. Number of Annual Reports submitted to FDA/CVM – 12

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.

Oxytetracycline (OTC) medicated feed INAD #9332 OTC formulation update: OTC INAD participants should please note that the OTC formulation for INAD #9332 has changed from Terramycin® 100 for Fish (TM 100) to Terramycin® 200 for Fish (TM 200). It is also important to note that TM 100 contains 100g of oxytetracycline per pound of Type A Medicated Article, and TM 200 contains 200g of oxytetracycline per pound of Type A Medicated Article. While INAD investigators are encouraged to use TM 200 for all future studies, stocks of TM 100 are still available in some locations (e.g., feed manufacturers) and may continue to be used until they are no longer available. Hence, the "take home message" is to please be sure to be aware of which Terramycin® product is being used in your studies, and to determine your dose calculations accordingly.

Additional information for OTC medicated feed INAD #9332 co-investigators: Given today's (9July 2008) news regarding the new OTC supplemental approval, INAD #9332 co-investigators will need to be aware that very shortly AADAP will be notifying all INAD #9332 participants of changes in the "conditions for use" under the INAD. In essence, those uses now newly approved will no longer be permitted under INAD #9332 authorization. Watch your mail or email for detailed information from AADAP.

FEATURE ARTICLE

AQUI-S® as a zero-withdrawal anesthetic: What happened on the way to a New Animal Drug Application, and where do we go from here?

Thomas Bell and David Erdahl

U.S. Fish and Wildlife Service,
Aquatic Animal Drug Approval Partnership Program
4050 Bridger Canyon Road,
Bozeman, Montana 59715, USA

Obtaining an FDA-approved zero-withdrawal anesthetic for use in freshwater fish has been a major focus of U.S. public sector aquaculture for more than a decade. Although MS-222 (tricaine methanesulfonate) is FDA-approved in the U.S. and has a long track record of efficacious and safe use, its approved label uses are limited. In particular, and as it relates to this discussion, food fish treated with MS-222 must be held for a minimum of 21 days following treatment before they can be released for legal harvest or slaughtered for food. By definition, food fish are any-and-all fish potentially available for human consumption, including fish stocked/released for resource management purposes. In contrast, a zero-withdrawal anesthetic would allow food fish to be released, stocked, or slaughtered "immediately" following treatment. In numerous fisheries management programs, and particularly those involving wild-stock population assessment and evaluation, there is a critical need for such an anesthetic. Hence, the impetus behind the past and ongoing search for a zero-withdrawal fish anesthetic.

Collaborative efforts to find a candidate potential zero-withdrawal anesthetic first began in earnest in the late 1980's and early 1990's. Although a logical strategy might have been to generate additional data that would permit the withdrawal period for MS-222 to be reduced from 21 days to zero days, advice from experts suggested that such an approach could be fraught with high, if not insurmountable, hurdles. It was also suggested that "re-opening" the MS-222 file could in fact potentially jeopardize the existing approval for MS-222. Consequently, a compound related to MS-222, benzocaine, was identified as the best candidate zero-withdrawal anesthetic.

Benzocaine was perceived by the aquaculture drug research community as being potentially "approvable" for a number of reasons. First and foremost it was a drug presumed to be safe (from a human food safety perspective) based primarily on its history of wide use in human medicine, including several over-the-counter oral local anesthetics (e.g., Anbesol® and Orajel®). Additionally, preliminary studies indicated that it was not only an effective fish anesthetic, but that is was also safe to target species (i.e., fish). As a result, benzocaine was selected by the Association of Fish and Wildlife Agencies' Drug Approval Project (AFWA Project, representing all 50 state fish and game agencies, USGS, USDA, and USFWS) as the priority anesthetic of choice, and work was initiated to generate all data needed to complete a New Animal Drug Application (NADA) for its use as a zero-withdrawal fish anesthetic. Work on benzocaine began in earnest in 1994, and as a result of these efforts key toxicology and residue chemistry components of the NADA were completed. However, while research efforts progressed in a positive direction, one major piece of the benzocaine NADA puzzle remained missing, i.e., a pharmaceutical sponsor for benzocaine had not been identified.

An NADA can not be submitted by anyone other than a U.S. pharmaceutical company (or their U.S. representative) intending to label and market a new animal drug. Although no pharmaceutical sponsor for benzocaine had "stepped-up to the plate" when NADA research efforts were first initiated, it was hoped that as data were generated with public funds and progress

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was made, a sponsor would be found. Unfortunately, as of late 1996 benzocaine was still officially "sponsorless."

At approximately this same time, a "brand new" potential zero-withdrawal anesthetic appeared on the drug radar screen. A company named AQUI-S New Zealand, Ltd. had a fish anesthetic product called AQUI-S® that was/is already approved for use in food fish as a zero-withdrawal product in New Zealand and several other countries. The active ingredient in AQUI-S® was/is isoeugenol, which was/is listed in the U.S. Code of Federal Regulations as a compound "Generally Recognized as Safe" (GRAS) by FDA for specific uses including use as a flavor enhancer in food for human consumption. Although appearances can be deceiving (keep reading), it appeared to many folks in the aquaculture drug approval consortium that gaining FDA-approval of AQUI-S® ought to be a cinch…..relatively speaking, of course. Perhaps most importantly, AQUI-S New Zealand, Ltd. was VERY interested in sponsoring an NADA for AQUI-S® use in the U.S. Consequently, the federal/state aquaculture drug approval consortium (i.e., AFWA Project), was faced with making a difficult but important decision…do we 1) continue work on benzocaine (for which several of the key and expensive toxicology and residue chemistry components have been completed, but remains without a pharmaceutical sponsor); or 2) switch horses in mid-stream and redirect resources to AQUI-S® (which has an interested sponsor, existing foreign approvals, and a GRAS designation by FDA, but for which no U.S. safety or effectiveness studies have been completed)?

In 1997, a survey was sent out to all AFWA Project stakeholders (including all 50 state fish and game agencies) describing in detail the benzocaine versus AQUI-S® dilemma as described in brief above. Results of the survey overwhelmingly supported hooking the AFWA Project wagon to the new horse…i.e., AQUI-S®. And during the next ~10 years, steady and significant progress was made towards assembling an AQUI-S® NADA package that would support FDA approval for its use of as a zero-withdrawal anesthetic in all freshwater reared finfish. Accomplishments included completion of the entire efficacy technical section, and major portions of the manufacturing/chemistry, human food safety, environmental safety, and target animal safety technical sections. Although AQUI-S® was truly on the home-stretch to an initial approval, all efforts and ongoing research came to a screeching halt in April/ May 2007.

Approximately 2-3 years earlier (i.e., 2004-2005) isoeugenol (the active ingredient of AQUI-S®) had been accepted by the National Toxicology Program (NTP; a program of the U.S. Department of Health and Human Service's National Institute of Environmental Health Sciences) as a candidate compound for extensive toxicological testing. In April 2007 *preliminary findings* from short-term acute (90 day) and long-term chronic (2 year) rodent carcinogenicity studies were made publically available in a NTP draft report. In one study of the chronic study set, the data indicated that male mice gavage-fed isoeugenol developed a statistically higher incidence of malignant lesions including hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined), than non-treated control animals. Although as stated above these results were considered to be preliminary and not final published NTP findings, they effectively forced the AFWA Project to put all ongoing AQUI-S® efforts on-hold. Additionally, the FWS voluntarily suspended all use of AQUI-S® under INAD 10-541 until further notice.

In late February 2008, after a year-long delay since the public release of the preliminary draft NTP report, the official NTP review board convened a meeting to allow for public input regarding the findings and conclusions published in the draft report. Although the draft report conclusions were challenged, including a challenge from a representative from AQUI-S New Zealand, Ltd. noting that isoeugenol used in the NTP toxicology studies, due to its age (5-7 years old at the time of testing), may have comprised study results, the board rejected all challenge arguments and stood by the conclusions stated in their draft report. The following "Conclusions" section has been excerpted from the draft abstract for the isoeugenol NTP study set entitled: *"Toxicology and Carcinogenesis Studies of Isoeugenol (CAS No. 97-54-1) in F344/N Rats and B6C3F1 Mice (Gavage Studies)."*

> ***"CONCLUSIONS***
>
> *Under the conditions of these 2-year gavage studies, there was* ***equivocal evidence***[1] *of carcinogenic activity of isoeugenol in male F344/N rats based on increased incidences of rarely occurring thymoma and mammary gland carcinoma. There was* ***no evidence***[2] *of carcinogenic activity of isoeugenol in female F344/N rats administered 75, 150, or 300 mg/kg. There was* ***clear evidence***[3] *of carcinogenic activity of isoeugenol in male B6C3F1 mice based on increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined). There was* ***equivocal evidence***[1] *of carcinogenic activity of isoeugenol in female B6C3F1 mice based on increased incidences of histiocytic sarcoma.*

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> *Exposure to isoeugenol resulted in nonneoplastic lesions of the nose in male and female rats and the nose, forestomach, and glandular stomach in male and female mice."*

Footnotes to excerpted conclusions:

1. "***Equivocal evidence*** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related."
2. "***No evidence*** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms."
3. "***Clear evidence*** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (a) increase of malignant neoplasms, (b) increase of a combination of malignant and benign neoplasms, or (c) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy."

Although for the lay-person (including FWS personnel!) the NTP conclusions may be somewhat difficult to fully interpret, the bottom-line is quite simple…i.e., *the NTP concluded that isoeugenol demonstrated clear evidence of carcinogenic activity*…period…end of discussion.

Following the NTP findings, FDA notified the FWS that effective immediately that they were rescinding all investigational food use authorizations under AQUI-S® INAD 10-541 (i.e., AQUI-S® could no longer be used to anesthetize food fish under INAD authorization). FWS/AADAP subsequently released several notices via our Newsletter and Website pertaining to this change in INAD 10-541 authorization status. Note: If you have any questions regarding these actions by the FDA and AADAP, please do not hesitate to contact Dave Erdahl (phone 406-994-9904, email dave_erdahl@fws.gov).

In late March 2008, the AFWA Project's Drug Approval Working Group (DAWG) held its Spring Meeting in Phoenix, AZ. At most bi-annual DAWG meetings discussion is split rather evenly between all AWFA Project priority drugs. Not surprisingly, this meeting was focused almost entirely on AQUI-S®, the NTP findings, and "now what?" Although discussion certainly explored any-and-all possible avenues to save, rescue, or somehow resuscitate AQUI-S®, the end result of discussion was a unanimous vote to suspend indefinitely all activities related to the approval of AQUI-S® as a zero-withdrawal anesthetic.

In spite of this monumental and totally unforeseen set-back, our collaborative quest for a zero-withdrawal anesthetic continues … we have not given up yet. As discussed at the DAWG meeting described above, the need for a zero-withdrawal anesthetic for use in domestic aquaculture remains a top DAWG (no pun intended!) priority. Rest assured that the DAWG is currently in the process of identifying the most suitable replacement for AQUI-S® as a zero-withdrawal anesthetic, and is searching high-and-low to find a pharmaceutical company willing (and financially able) to sponsor the NADA. Although several potential candidate compounds have already been identified, and a number of potential sponsors contacted, it would be premature to discuss these activities more specifically until such time as we have had the opportunity to evaluate the pros and cons of all options more thoroughly. Please take our word for it that the DAWG is working diligently, and hand-in-hand with FDA, to determine the best possible replacement compound for AQUI-S®.

Stay tuned … as soon as a candidate drug and potential pharmaceutical sponsor have been identified, we will relay that information to you via the AADAP Website and Newsletter. Hopefully, we will be able to share more positive information with you soon!

RELEVANT LITERATURE

The following is a list of journal publications with particular relevance to the broad topic of chemotherapy in aquaculture. This list, like that from the last issue of the AADAP Newsletter, comprises citations from 2007 and 2008. Please note that this list does not include those provided in the previous issue of the AADAP Newsletter.

If you have come across literature that you believe would be of interest to the readership of the AADAP 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 AADAP Newsletter does not imply: (1) recommendation of the technique to any particular situation, (2) concurrence with a treatment procedure/drug, (3) acceptance by 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.

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Barnes, M, and CA Soupir. 2007. Evaluation of formalin and hydrogen peroxide treatment regimes on rainbow trout eyed eggs. *North American Journal of Aquaculture* **69(1):**5-10.

Barry, TP, et al. 2007. Stability of 17-alpha-methyltestosterone in fish feed. *Aquaculture* **271(1-4):**523-529.

Bosworth, BG, et al. 2007. Effects of rested-harvest using the anesthetic AQUI-S® on channel catfish, *Ictalurus punctatus*, physiology and fillet quality. *Aquaculture* **262(2-4):**302-318.

Crook, DA, et al. 2007. Production of external fluorescent marks on golden perch fingerlings through osmotic induction marking with Alizarin Red S. *North American Journal of Fisheries Management* **27(2):**670-675.

Du, H, et al. 2007. Anesthetic effects of MS-222, clove oil, and benzocaine on cultured American shad *Alosa sapidissima*. *Journal of Dalian Fisheries University* **22(1):**20-26.

Guenette, SA, et al. 2007. Pharmacokinetics of eugenol in rainbow trout (*Oncorhynchus mykiss*). *Aquaculture* **266(1-4):**262-265.

Harper, C. 2007. Chemical resistance of 19 pathogens in aquaculture. *Aquaculture Magazine* **33(2):**40.

Ingram, B, et al. 2007. Breeding performance of Malaysian mahseer, *Tor tambroides* and *T. douronensis* in captivity. *Aquaculture Research* **38(8):**809-818.

Lahnsteiner, F, and T Weismann. 2007. Treatment of Ichthyophthiriasis in rainbow trout and common carp with common and alternative therapeutics. *Journal of Aquatic Animal Health* **19(3):**186-194.

Leef, MJ, et al. 2007. The respiratory effects of chloramine-T exposure in seawater-acclimated and amoebic gill disease-affected Atlantic salmon Salmo *salar*. *Aquaculture* **266(1-4):**77-86.

Mauk, R. 2008. Efficacy of oxytetracycline marking of fingerling palmetto bass in hard water. *North American Journal of Fisheries Management* **28(1):**258-262.

Miranda, CD, and R Rojas. 2007. Occurrence of florfenicol resistance in bacteria associated with two Chilean salmon farms with different history of antibacterial usage. *Aquaculture* **266(1-4):**39-46.

Orr, C. 2007. Estimated sea louse egg production from Marine Harvest Canada-farmed Atlantic salmon in the Broughton Archipelago, British Columbia, 2003 – 2004. *North American Journal of Fisheries Management* **27(1):**187-197.

Rasowo, J, et al. 2007. Effects of formaldehyde, sodium chloride, potassium permanganate, and hydrogen peroxide treatment on hatch rate of African catfish *Clarias gariepinus* eggs. *Aquaculture* **269 (1-4):**271-277.

Ross, LG, et al. 2007. Anaesthesia, sedation, and transportation of juvenile *Menidia estor* (Jordan) using benzocaine and hypothermia. *Aquaculture Research* **38(9):**909-917.

Tabandeh, MR, and M Akhlaghi. 2007. Efficacy of conventional disinfectants on isolated *Streptococcus iniae* from diseased rainbow trout in laboratory and culture tank conditions. *Iranian Scientific Fisheries Journal* **16(3):**29-38.

Taylor, PW, and RA Glenn. 2008. Toxicity of five therapeutic compounds on juvenile salmonids. *North American Journal of Aquaculture* **70(2):**175-183.

Wagner, EJ, et al. 2008. Comparison of the efficacy of iodine, formalin, salt, and hydrogen peroxide for control of external bacteria on rainbow trout eggs. *North American Journal of Aquaculture* **70 (2):**118-127.

Westcott, JD, et al. 2008. Optimization and field use of a bioassay to monitor sea lice *Lepeophtheirus salmonis* sensitivity to emamectin benzoate. *Diseases of Aquatic Organisms* **79(2):**119-131.

USGS's CORNER

UMESC collaborates with local university to support aquaculture drug research (contact M. Gaikowski, mgaikowski@usgs.gov)**:** UMESC recently entered into a cooperative research agreement with Winona State University (WSU) to develop three student-led projects to develop data to support aquaculture drug approvals. The first two projects are focused on the development of data sets to support the environmental assessment of erythromycin thiocyanate (ERTT), the active ingredient in Aquamycin 100®. The first research project is the development of physical-chemistry data for ERTT and to describe its transformation in freshwater. Literature values for basic physical chemistry parameters are nearly nonexistent for ERTT, primarily only available for the erythromycin products used for human or large animal medicine. In collaboration with UMESC scientists Jeff Meinertz and Jeff Bernardy, WSU student Davyion Crossland is developing water solubility, water-octanol coefficient, dissociation constants, and transformation rate information for ERTT and its transformation product deanhydroerythromycin. Similarly, WSU student Sevwandie Liyanarachchi is developing information on

(Continued from page 8)

the microbial toxicity of ERTT and deanhydroerythromycin. Combining the information from the two research projects should enable an accurate environmental assessment of the use of ERTT in aquaculture. Data development for both projects is expected to be complete by August 2008.

The third WSU project is the development of divergent sets of statistical analyses by WSU student Silas Bergen. Silas, a senior math major, is developing statistical analyses for data sets ranging from pivotal INAD mortality data sets provided by AADAP from hatcheries conducting pivotal efficacy studies to analyses of Daphnia mortality, brood production, and growth to analysis of lake sturgeon avoidance behavior associated with exposure to lampricides.

UMESC research on environmentally-present pharmaceuticals collaterally supports erythromycin thiocyanate environmental assessment. (contact J. Meinertz, jmeinertz@usgs.gov)

The St. Croix National Scenic Riverway is classified as an Outstanding Resource Waterway by the states of Minnesota and Wisconsin. The National Park Service has concerns about the impact that pharmaceutical and personal care products (PPCP) may be having on the aquatic invertebrate community in the Riverway. This study was designed to determine the effects 2 PPCP found or most likely found in the St. Croix National Scenic Riverway have on a chronically exposed aquatic invertebrate. The PPCP evaluated were diphenhydramine hydrochloride and erythromycin thiocyanate. Diphenhydramine hydrochloride is the active ingredient in the over-the-counter antihistamine, Benadryl®. Diphenhydramine hydrochloride was detected in a water sample taken from the Riverway downstream from a wastewater treatment plant near a mussel bed known to include the federally listed endangered Higgins' eye pearly mussel *Lampsilis higginsi* and the winged-maple leaf mussel *Quadrula fragosa*. Erythromycin thiocyanate is the active ingredient in Aquamycin 100® which is presently under investigation for use in aquaculture to control mortality caused by bacterial kidney disease. A key data point presently lacking from the erythromycin thiocyanate environmental assessment is an assessment of the potential impacts on aquatic invertebrates. Though various forms of erythromycin have been used for the treatment and prevention of human and animal diseases for several decades, sufficient toxicological information is not available to assess its potential impacts to aquatic invertebrates. Erythromycin was detected in the effluents from undisclosed wastewater treatment plants discharging directly into undisclosed Wisconsin surface waters.

The study was conducted with 8 treatment groups with 7 test chambers per treatment. One <24 h old *Daphnia magna* was distributed to each chamber at the start of the study and were then continuously exposed for 21 days in a flow-through test system. Survival, production, and length (Figure 1) data are presented in Table 1.

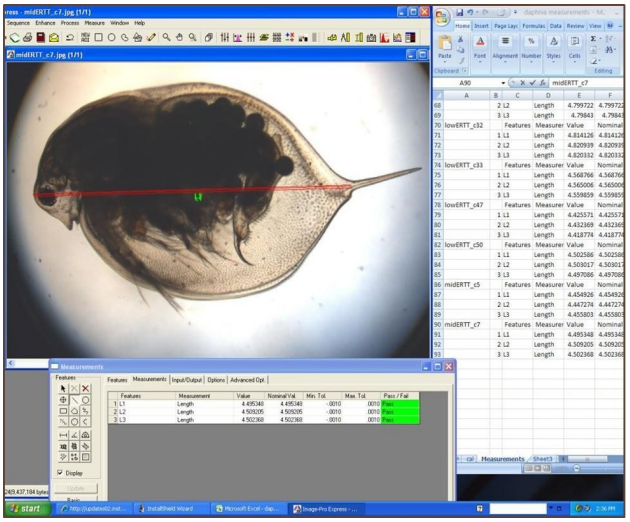

Figure 1. Photomicrograph of a Daphnia during processing in image-analysis software to measure growth (length; top of the head to the base of the spine).

Treatment group (µg/L)	Number surviving	Total offspring	Mean length (mm)
control	6 of 7	1071	4.467
0.12 DH	7 of 7	1207	4.548
71 DH	0 of 7	0	-
850 DH	0 of 7	0	-
0.45 DH	7 of 7	1328	4.601
250 DH	6 of 7	1100	4.46
3000 DH	1 of 7	247	4.424
84 DH 320 DH	0 of 7	0	-

Table 1. Adult survival, reproduction and growth of *Daphnia magna* following 21-d exposure to diphenhydramine hydrochloride (DH) and/or erythromycin thiocyanate (ET).

UMESC confirming saprolegniosis infection model in freshwater fish (contact M. Tuttle, mtuttle@usgs.gov): UMESC is confirming immersion challenge models in walleye and rainbow trout to use to evaluate the efficacy of external fungicides to control mortality associated with saprolegniasis. *Saprolegnia diclina* and *S. parasitica* were obtained from the American Type Culture Collection and subcultured at UMESC for use in the challenge trials. Two trials were

conducted to evaluate mortality patterns from walleye and rainbow trout challenged with either *S. diclina* or *S. parasitica* by immersion bath following abrasion with either dry-wall sanding screen or Dremel® tool. Rapid and complete mortality occurred in walleye challenged with *S. diclina* after dry-wall sanding screen abrasion with 100% mortality 4 d after challenge. When challenged with *S. diclina* following Dremel® tool abrasion, both walleye and rainbow trout developed clinical signs consistent with saprolegniosis and produced mortality patterns similar between the two species (Figure 1).

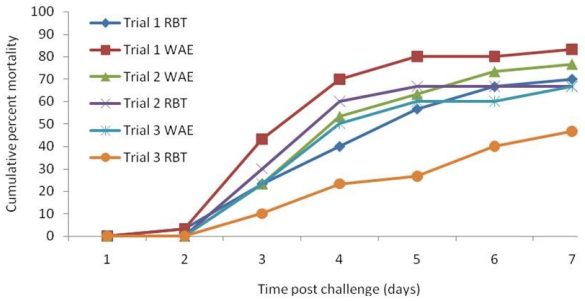

Figure 1. Cumulative percent mortality of walleye and rainbow trout following Dremel® tool abrasion and immersion challenge with *S. diclina* for 6 hours.

A third trial was conducted to evaluate abrasion consistency when using the Dremel® tool, the effect of immersion bath challenge duration and the effect of zoospore concentration on cumulative mortality and time to onset of mortality. Walleye and rainbow trout were challenged with *S. diclina* for 2, 4 or 6 hours in challenge baths inoculated with either 5 or 10 *S. diclina*-infected hemp seeds/L. Previous trials had confirmed the relationship between zoospore (colony-forming units) concentration and the number of hemp seeds/L in the challenge bath. Mortality patterns were similar for both walleye and rainbow trout challenged for either 4 or 6 h in challenge baths inoculated with 10 hemp seeds/L (Figure 2); onset of clinical signs and mortality (Figure 2) were similar to trials 1 and 2 and consistent with those previously reported by Jeff Rach in rainbow trout and channel catfish and Renate Reimschuessel in rainbow trout.

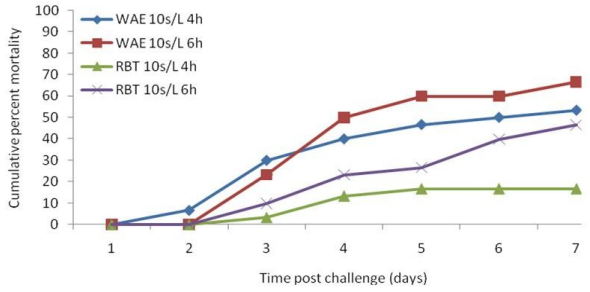

Figure 2. Cumulative percent mortality of walleye and rainbow trout following Dremel® tool abrasion and immersion challenge with *S. diclina* for 4 or 6 hours.

Our trial results suggest that Dremel® tool abrasion combined with immersion challenge with either *S. diclina* or S. *parasitica* at 10 seed/L for either 4 or 6 h should produce mortality patterns suitable for the development of effectiveness data. An efficacy protocol has been drafted and is presently in review to evaluate the efficacy of 35% PEROX-AID® to control mortality associated with saprolegniosis caused by either *S. diclina* or *S. parasitica* infection induced using these challenge methods.

UMESC welcomes new Fish Culturist (contact S. Redman, sredman@usgs.gov)**:** UMESC is pleased to welcome Steve Redman back to its staff as the new Center Fish Culturist. Steve re-joined UMESC and the U.S. Geological Survey on June 9, 2008. Steve had last worked as the lead Fishery Biologist at the U.S. Fish and Wildlife Service's Iron River National Fish Hatchery in Iron River, WI. Steve worked at Iron River since transferring there from UMESC in the fall of 1998. While at Iron River, Steve was in charge of the salmonid production program, evaluating feeding regimens, managing fish loading densities and inventories, and fish health assessments. While involved in salmonid production from egg take to distribution (of ~3.5 million lake trout and ~100,000 coaster brook trout), Steve was also the station safety officer and was the station youth program coordinator.

Prior to his employment at Iron River, Steve worked at UMESC from June 1991 until transferring to the FWS in 1998. During his tenure at UMESC, Steve participated in a number of studies, ranging evaluations of aquaculture drugs to field and laboratory toxicity assessments of fishery management chemicals to aquatic nuisance species and to non-target organisms. During the last 4 years of his time at UMESC, Steve assisted Lynn Lee in managing UMESC's Fish Culture program. Steve's previous laboratory experience conducting research under Good Laboratory Practice regulations and his wealth of experience gained at Iron River make him an excellent addition to UMESC and to support UMESC research on aquaculture drugs, fishery management chemicals, and aquatic invasive species.

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

The SNARC crew has been extremely busy with catfish spawning season and it's almost over. We're looking at the effectiveness of several therapeutants on water molds (i.e., fungus) that grow on catfish egg masses. This year we did some studies with copper sulfate, hydrogen peroxide and diquat.

The effectiveness and target animal safety research studies for the copper sulfate label claim for catfish egg

fungus have been completed successfully. Journal articles and final study reports are a priority. When these have been accepted by CVM, the only major technical section remaining will be Environmental Assessment. These will be addressed soon.

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

MEETINGS, ETC.

Symposium on Immunity and Disease Resistance in Fish; 28 July - 1 August 2008; Portland, Oregon, USA: This symposium is being held as part of the 8th International Congress on the Biology of Fish. The symposium is being organized by Drs. Stephen Kaattari (Virginia Institute of Marine Science, College of William and Mary, Gloucester Point, VA), and Gregory Wiens

(U.S. Department of Agriculture, National Center for Cool and Cold Water Aquaculture, Kearneysville, WV). The symposium is described as such: "Critical to the survival of any species is the optimal operation of their immune defense systems. Although fish have set the evolutionary paradigm for the evolution of all vertebrate immune systems, they possess and retain mechanisms unique to their own physiology, anatomy and environment. Facets of immune function span and integrate a variety of disciplines from endocrinology and neurophysiology to toxicology and microbiology. The last two decades have demonstrated the extraordinary nexus that immunology serves within these sub-disciplines of ichthyology. This section will focus on the current molecular, cellular, and genetic means of understanding and enhancing fish immunity, both as a basic science and for the improvement of aquaculture." More detailed information on the International Congress and the symposium, including registration, accommodations, etc., can be accessed by clicking here.

Australasian Aquaculture 2008 International Conference & Trade Show; 3-6 August 2008; Brisbane, Queensland, Australia: Australasian Aquaculture 2008 is the joint international conference, trade show and series of associated events of the National Aquaculture Council, the Asian Pacific Chapter of the World Aquaculture Council and the Australian Prawn Farmers Association. Skretting and the Fisheries Research and Development Corporation are co-sponsors of the event. The conference takes place in the Brisbane Convention & Exhibition Centre. Detailed information regarding the conference and trade show can be found by clicking here.

138th Annual Meeting of the American Fisheries Society; 17-21 August 2008; Ottawa, Canada: This year's meeting of the American Fisheries Society is being held at the Ottawa Congress Centre and Westin Hotel, in Ottawa, Ontario, Canada. The theme of the meeting is "Fisheries in Flux: How Do We Ensure Our Sustainable Future". This theme reflects President Mary Fabrizio's Program of Work for her year in office, and addresses the ongoing challenge of confronting change when managing fisheries. For detailed information see the Conference website (http://www.fisheries.org/afs08/) or click here.

International Conference on Fish Diseases and Fish Immunology; 6-9 September 2008; Reykjavik, Iceland: The understanding of infectious fish diseases and the causative agents, like viruses, bacteria and parasites, has been growing fast lately in the international scientific society. In parallel there is an increasing knowledge on host-pathogen interaction, including fish immunology and genome analysis of pathogens and several fish species. The aim of the meeting is to gather scientists from Europe and other parts of the world to discuss the recent developments in the field. Sessions will include fish immunology, viral diseases of fish and causative agents, bacterial diseases of fish and causative agents, fish parasitology, communication networks in marine bacteria and diseases in coldwater fish species. For more information refer to the conference website, by clicking here.

Aquaculture Europe 2008; 15-18 September 2008; Krakow, Poland: Aquaculture Europe 2008 is the second of the "new format" Aquaculture Europe events, that combines a scientific conference with a trade exhibition. The theme of AE2008, "Resource Management," addresses the natural, human and material resources for the sustainable development of aquaculture. As an example, the Water Framework Directive (2000/60/E) is the most substantial piece of water legislation ever produced by the European Commission. It requires that all inland and coastal waters within defined river basin districts must reach at least good status by 2015 and defines how this should be achieved through the establishment of environmental objectives and

ecological targets for surface waters. This will be just one focus of AE2008. For more information refer to the conference website by clicking here.

International Council for the Exploration of the Sea - Annual Science Conference; 22-26 September 2008, Halifax, Nova Scotia, Canada: The theme for Session "D" of the conference is: New Trends in Diseases of Marine Organisms: Causes and Effects. Abstracts for oral and poster presentations will be considered for Theme Session D on the following and other relevant subjects: a) causes and effects of emerging diseases (including parasites) in wild fish, shellfish and other marine organisms; b) causes and effects of new diseases (including parasites) in farmed fish and shellfish; c) the use of diseases and parasites of wild marine organisms as indicators in integrated ecosystem health monitoring and assessment; d) new trends in the disease interactions between wild and farmed fish and shellfish; e) effects of introduced species on the health status of native fish and shellfish stocks; and f) new methodologies related to disease diagnosis and control. On-line abstract submission is now available at the ICES ASC website: http://www.ices.dk/iceswork/asc/2008/index.asp. Abstract are due: 21 April 2008. For further information contact: Sharon MacLean (sharon.maclean@noaa.gov), Thomas Lang (thomas.lang@vti.bund.de) or Sharon McGladdery (mcgladderys@inspection.gc.ca).

Aqua 2008 - 10th Congress of Equadorian Aquaculture and Trade Show; 6-9 October 2008; Guayaquil, Ecuador: This three-day conference and trade show is being held at the new Convention Center ExpoGuayaquil. Technical sessions include those on: aquaculture diversification, shrimp health and diseases, shrimp culture and markets. Detailed information on registration, accommodations, etc. can be found on the conference website or by clicking here.

5th International Symposium of the Japanese Society of Fish Pathologists; 18-19 October 2008; Tokyo, Japan: The theme of this year's international symposium is "The role of fish pathology in sustainable aquaculture." This year's symposium is being held at The University of Tokyo's Yayoi Auditorium in Bunkyo, Tokyo, Japan. The official language of the symposium is English. Keynote topics include: emerging diseases, international trade of aquatic organisms, international epidemiology and disease control. The deadline for submission of abstracts and early registration is 31 May 2008. For registration, accommodation and all other detailed information, click here to access the conference website.

ROZ's CORNER

Progress on chloramine-T (Halamid® Aqua+): Two initial label claims are close to completion: control of mortality due to 1) bacterial gill disease on all freshwater-reared salmonids and 2) external columnaris disease on walleye and possibly largemouth bass

On 19 May 2008, Axcentive SARL submitted the complete Chemistry, Manufacturing, and Controls Technical Section on Halamid® Aqua+ to CVM for review. On 23 May 2008, Axcentive SARL received word that CVM is requesting some minor changes to the labeling text. All the major technical sections have been submitted and most of them have been accepted.

Progress on 17α-methyltestosterone (17MT) (Masculinizing Feed for Tilapia®) - gender manipulation aid: One initial label claim in progress: 1) masculinization of female early life-stage tilapia

The North Central Regional Aquaculture Center (NCRAC) and Western Regional Aquaculture Center (WRAC) Boards of Directors (BOD) have jointly made the decision to fund two studies that are needed to complete the New Animal Drug Application for 17MT in tilapia: repeat of the 1) target animal safety study in tilapia and 2) the feed method transfer study. These studies will start no earlier than 1 September 2009.

In other developments on MT, CVM accepted the method validation study in water but not the validation in sediment as developed by University of Wisconsin - Madison (UW-M) and requested additional information from UW-M concerning the study report on the transformation of 17MT in aquatic-sediment systems (31 March 2008). On 8 April 2008, Rangen, Inc. submitted to CVM the data on stability, homogeneity, and segregation of 17MT feed based on studies by UW-M.

Supplemental approval imminent for oxytetracycline dihydrate (Terramycin® 200 for Fish): On 2 June 2008, Phibro Animal Health submitted the Administrative NADA for a supplemental approval of Terramycin® 200 for Fish for the following: control of mortality due to (1) columnaris disease in freshwater-reared *Oncorhynchus mykiss* and (2) coldwater disease in freshwater-reared salmonids. Phibro Animal Health will add the previously approved label claim (23 September 1970) for marking skeletal tissue of Pacific salmon to this labeling (250 mg of oxytetracycline per kg of fish per day in fish feed); it was never on any previous labels. Additionally, the temperature restriction on treating salmonids below 9° C. is removed from the label as a result of UMESC data. CVM has 60 days to review the NADA package.

This upcoming supplemental NADA approval is a result of the combined efforts of the following partners originally under the auspices of the Association of Fish and Wildlife Agencies, Federal-State Aquaculture Drug Approval Partnership Project: (1) AADAP (Effectiveness studies; Guidance #152); (2) UMESC (Environmental Safety; Effectiveness; and Human Food Safety to include analytical methodology, marker residue depletion studies, and Guidance #159); (3) National Aquaculture NADA Coordinator (coordination of approval-related activities; Guidance #159; collaborating with Phibro Animal Health on Labeling, All Other Information, Minor Use and Minor Species designation, and Administrative NADA); and (4) Phibro Animal Health (product chemistry changes; Guidance #152 and #159; Labeling, All Other Information, Minor Use and Minor Species designation; Administrative NADA).

Update on the formation of a new industry-driven group: Because the Joint Subcommittee on Aquaculture Working Group on Aquaculture Drugs, Biologics, and Pesticides (WGADBP) is being phased out due to conflicts with the Federal Advisory Committee Act, stakeholders has moved to form a new group tentatively named the National Aquaculture Industry Therapeutic Agent Program (NAI-TAP). The stakeholders convened a conference call on 24 April 2008 that produced the following major points:

- This new industry-oriented group would be broader in its approach that the WGADBP.
- Several alternative names for the group were discussed and an accurate descriptive title needs to be selected.
- Discussions centered on membership in NAI-TAP but no consensus was achieved.
- Participation at all levels will be easier if meetings are held in conjunction with other national meetings that industry, research scientists, producers and federal and state employees would normally attend.
- It was suggested that Roz Schnick serve as chair of the group with several volunteers to assist; she accepted as the will of the industry group. Several people offered to assist with implementing necessary actions.
- The primary activities of the group will revolve around sharing of ideas and information concerning the development and use of tools used in aquaculture with little, if any, emphasis on legislation, regulations, etc.
- Dues were discussed but no consensus was achieved.
- It was agreed that a website and a list server were needed for the group to function on a broad basis.
- It was also agreed that there needs to be a mechanism to ensure all aquaculture groups, companies, and agencies with interests in the mission, vision, and objectives be invited to be part of this group.
- A meeting is planned in Bozeman, Montana for 1 August 2008 to discuss finalizing this entity and planning the next steps and activities.

Update on candidate zero-withdrawal sedatives for aquatic food animals: In a 19 March 2008 conference call between UMESC, National Aquaculture NADA Coordinator, and CVM's Division of Human Food Safety, four potential candidates (benzocaine, eugenol, metomidate, and tricaine methanesulfonate), CVM indicated that at least some mammalian safety and residue chemistry studies would be needed to support a potential approval for a practical withdrawal period for one of these sedatives. The DAWG (Drug Approval Working Group of the Association of Fish and Wildlife Agencies) met on 26-28 March 2008 to discuss the available options for, and limitations to, an isoeugenol approval and to formulate plans to identify an alternative sedative. The DAWG held a conference call with CVM on 17 June 2008 to discuss the developments on candidate sedatives since the March DAWG meeting and agreed to have a meeting on 20 August 2008 to learn from CVM what definitive data requirements remain for approval for benzocaine, eugenol, and tricaine methanesulfonate (MS-222) to achieve a practical zero-withdrawal time as a sedative.

Update on Roz's website: The National Aquaculture NADA Coordinator requested help from AquaNic to change her website address to

http://aquanic.org/aquadrugs because USDA could no longer be involved because of the Federal Advisory Committee Act.

Rosalie (Roz) Schnick, National Coordinator for Aquaculture New Animal Drug Applications, Michigan State University, La Crosse, Wisconsin.

CVM's NOTES

The following personnel changes have or will take place at FDA's Center for Veterinary Medicine.

Dr. Donald Prater will be on detail as Acting Director of the Division of Therapeutic Drugs for Food Animals (June 8 through August 31, 2008) and then as Acting Director of the Scientific Support Staff (September 1 through December 20, 2008). During these times, Dr. Edward Chen and Dr. Jennifer Matysczak will be Acting Leader of the Aquaculture Drugs Team. Dr. Chen will be Acting Leader of the Aquaculture Drugs Team from June 8 through September 13, 2008. Dr. Matysczak will be Acting Leader of the Aquaculture Drugs Team from September 14 through December 20, 2008.

There have also been some personnel changes at CVM's Office of Minor Use and Minor Species Animal Drug Development (OMUMS). Congratulations to Dr. Meg Oeller, who was recently selected the new Director of OMUMS. Also, Dr. Joan Gotthardt has left her position as Director of the Division of Therapeutic Drugs for Food Animals and has joined OMUMS, working primarily on "Indexing."

Email addresses remain the same for individuals noted; e.g., firstname.lastname@fda.hhs.gov.

Dr. Jennifer Matysczak, Aquaculture Drugs Team, Office of New Animal Drug Evaluation, Center for Veterinary Medicine, Food and Drug Administration.