U.S. Fish & Wildlife Service

The Aquatic Animal Drug Approval Partnership Program

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

AADAP
Aquatic Animal Drug Approval Partnership Program

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Late spring on Georgetown Lake, Montana USA

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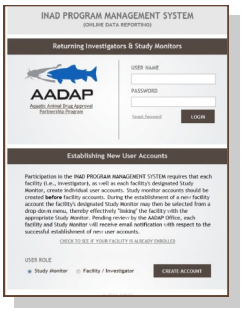
WHAT'S SHAKIN'

AADAP's INAD Program Management System (IPMS) is finally a reality: The USFWS-AADAP Program is proud to announce that it has finally made available to our current and prospective partners a totally web-based system to manage all aspects of our Investigational New Animal Drug (INAD) exemption program. The INAD Program Management System, or IPMS, replaces a paper-based system which was inherently inefficient, labor-intensive and often prone to recording and transcription errors.



The IPMS is entirely web-based; INAD program partners will now be able (and be required) to complete all "paperwork" associated with their use of investigational aquaculture drugs on a secure website. Not only will this eliminate AADAP's need to transcribe all data from paper forms to an electronic database, but it will minimize, and in most cases eliminate, recording and transcription errors. The IPMS has been designed with a maximum number of drop-down menus, error-checking features and automatic notifications of required actions, etc. to make the investigators' and monitors' recording tasks simpler and more accurate.

Although the IPMS has been several years in the making, this first version will likely not be without some bugs, for which we apologize. For more information on, and access to, the IPMS click here or copy this URL address (http://tinyurl.com/7tcqz79) into your browser. The link will take you to an IPMS page (on the AADAP Website), which includes links to the IPMS, an introductory letter and an IPMS User Manual.

The 18th Annual USFWS Aquaculture Drug Approval Coordination Workshop will be here in just a few months: La Crosse, Wisconsin USA will be the location for this year's annual Workshop. The good folks at the U.S. Geological Survey's Upper Midwest Environmental Sciences Center (UMESC) in La Crosse will be hosting the Workshop for a second time. Mark Gaikowski and the gang at UMESC, with logistic help from the folks at the University of Wisconsin - La Crosse's Continuing Education and Extension group have put together another excellent lineup of presentations/discussions reviewing the current status of aquaculture drug approval activities in the USA. The Workshop will be held on Tuesday, 31 July 2012. In addition to the Workshop, several other meetings are being held at the same venue immediately before and after the Workshop (see page 17 for a description of the other meetings). Most notable of the other meetings is the 2012 annual meeting of the American Fisheries Society's Fish Health Section (AFS-FHS). The AFS-FHS will kick off its meeting with a special session on topics related to aquaculture drug approval activities on Wednesday, 1 August from 8:00 am to 12:00 noon. For

more detailed information on the 18th Annual USFWS Aquaculture Drug Approval Coordination Workshop check AADAP's Website often.

Bibliography of aquaculture drug-related literature: Since the March 2008 issue of the AADAP Newsletter, we have included a section devoted to listing the results of our literature searches since the publication of the previous issue of the Newsletter. Basically our searches focus on as many keywords as we can come up with that link aquaculture species and drugs. In addition to the list in each Newsletter, we have compiled these all into one file which we maintain on our website. The current list contains in excess of 550 citations. For those interested, it is an Adobe PDF file and can be viewed or download by clicking here or at the following URL: http://www.fws.gov/fisheries/aadap/PDF/drug_related_literature%2014mar2012.pdf.

Early spring meeting planned between the American Fisheries Society and upper management from FDA's Center for Veterinary Medicine: In December 2011, an American Fisheries Society (AFS) Policy Statement entitled ***"Need for an Immediate-Release Anesthetic/Sedative for Use in the Fisheries Disciplines"*** was adopted by AFS membership (~97% of votes cast were in favor of adopting the policy). At about this same time, the AFS Governing Board and Resource Policy Committee were discussing how to make better use of AFS policy statements. The reasoning for these discussions being that if an issue was important enough to dedicate the time and resources to develop a policy statement, then wasn't it of at least equal importance to make sure that others were allowed the opportunity to give serious thought and consideration to the content of the policy statement?

Hence, in the case of the immediate-release fish sedative policy statement, several actions have been initiated that are hoped will raise awareness of the need for such a sedative by fisheries professionals. A press release was developed and sent to various media outlets to announce the new policy, and a manuscript summarizing the content of the policy statement is being developed and will soon be submitted to the *Transactions of the American Fisheries* Society journal to be considered for publication.

In addition, a letter was written by members of the AFS Resource Policy Committee, signed by Dr. Gus Rassam (AFS; Executive Director), and sent to Dr. Bernadette Dunham (FDA's Center for Veterinary Medicine; Director) and Dr. Steve Vaughn (CVM; Director of the Office for New Animal Drug Evaluations) requesting a meeting to discuss the policy statement and associated issues in more detail, and to offer the AFS's help assisting FDA in charting a reasonable course to increase the availability of safe and effective fish sedatives. All were delighted when news was received from Dr. Rassam and Kevin Lynch (AFS; Policy and Development Coordinator) that Drs. Dunham and Vaughn would like to schedule a meeting to discuss this issue. Tentatively this meeting is been planned for sometime is early spring. Scheduling such a meeting with CVM's upper management is not a simple task due to the demands on their time. However, it is most certainly appreciated that they are willing to meet in spite of the demands on their time with issues that are likely of internal higher priority than drug approvals for minor species. Dr. Jen Matysczak (CVM; Aquaculture Team Leader) has been tasked with logistically scheduling the meeting, and Jim Bowker (AADAP and AFS Fish Culture Section President) has been providing her with agenda items to be discussed during the meeting. Specific agenda items will focus on potentially revising data requirements for approval of AQUI-S®20E (10% eugenol) and BENZOAK® (20% benzocaine) based on: their active ingredient, the sedative use-pattern, the flexibility on how the products can be used and disposed of, and the experience of the fisheries professionals who will be using the products. In addition, the hope is that there will be the opportunity to talk about how studies (e.g., efficacy, safety and residue chemistry) can be designed to address multiple label claims (e.g., light sedation for transport, heavy sedation for handling and anesthesia for surgery).

As per our request, Dr. Matysczak is also scheduling additional time for an informal meeting such that AFS representatives may meet with Drs. Dunham and Vaughn. The purpose of this second meeting is to discuss the general challenges the aquaculture community faces trying to get drugs approved for a minor species, and the concern that folks are packing-up and walking away from the process – not just sponsors and researchers, but end-users as well.

We applaud those at CVM who have embraced the challenge to explore alternatives to the "status quo" approach to gaining new approved drugs for minor species. We also acknowledge that some recent CVM decisions (based on previously submitted data and information) have resulted in a reduction (yes, a reduction!!) in the number of studies, or data to be collected in specific studies – and we are extremely encouraged by these new and non-traditional approaches to meeting data requirements. It is certainly our hope that others within CVM will consider similar approaches to completing other/additional technical section data requirements. This in turn would allow fisheries management professionals to gain legal access to effective and safe sedatives for sedated fish to be immediately released back into the wild.

We've all got out fingers crossed…and look forward to productive discussion at the upcoming meeting.

AADAP DRUG UPDATES

General: Over the years, we have found that during the winter months we 1) typically hunker down and draft Final Study Reports (FSRs) for submission to the U.S. Food and Drug Administration's Center for Veterinary Medicine (CVM), and 2) hopefully find the opportunity to launch a target animal safety (TAS) study or two. This winter, we focused on writing up FSRs for studies conducted last fall demonstrating the effectiveness of AQUI-S®20E (10% eugenol) and BENZOAK® (20% benzocaine) to sedate fish to handleable. Writing–up the results of these studies has been a HUGE project, but we're almost done (more information on this topic below). Although it is getting pretty late in the winter season and we have yet to launch a TAS study, we believe we have a pretty good excuse. With significant help from U.S. Fish & Wildlife Service's Bozeman Fish Technology Center hatchery staff we spent quite a bit of time pretty well gutting, redesigning, retrofitting and generally "modernizing" the AADAP Drug Research wet-laboratory. Out went the old aluminum rectangular tanks, packed columns, head-boxes for mixing cold and warm spring water and the open drain system. In went a vacuum degassing chamber, flow meters, space-saving circular tanks, UV disinfection (coming soon), and a closed drain system. The new system is quiet and clean, and we're anxious to get a study or two up and running in the new system. Additional information on upcoming TAS studies is provided in the drug updates below.

AQUI-S®20E and BENZOAK® Update:

A whole bunch of efficacy studies: In the last AADAP Newsletter, we described a series of studies conducted in September 2010 at Southern Illinois University-Carbondale (SIU-C; Carbondale, Illinois USA) and the U.S. Geological Survey's Upper Midwest Environmental Sciences Center (UMESC; La Crosse, Wisconsin USA). These studies were designed to generate data to evaluate the effectiveness of AQUI-S®20E and BENZOAK® to independently sedate nine different fish species to the handleable stage. We were at each facility for a week, and were assisted tremendously by Dr. Jesse Trushenski and her graduate students at SIU-C and Jeff Meinertz and his colleagues at UMESC. The results of the these studies demonstrated that both drugs effectively sedated the following fish species to handleable: hybrid striped bass, blue catfish, channel catfish, brown trout, lake trout, common carp, fathead minnow, yellow perch, and walleye. The excitement of what we were able to accomplish during out visits was quickly tempered by the fact that we'd have to write up all the data and submit FSRs to CVM for review. Thanks to the efforts of AADAP'ers Molly Bowman, Niccole Wandelear, and Dan Carty, the last of the 24 FSRs should be submitted to CVM's Aquaculture Team by the end of March.

Upcoming target animal safety studies: In anticipation that no additional studies will be required to demonstrate that BENZOAK® and AQUI-S®20E are effective sedatives, we have turned our attention to conducting the target animal safety (TAS) studies (three for each drug) required to be completed before the drugs can gain CVM approval. TAS studies are conducted to establish the margin of safety (i.e., difference between the highest non-toxic effective dose and lowest toxic dose) as determined by overdosing (i.e., concentration) and overexposing (i.e., time). Current plans are to conduct TAS studies on rainbow trout, channel catfish, and a representative coolwater fish species for each sedative.

Target animal safety studies can be technically more demanding than efficacy studies, especially as it pertains to sedatives. However, we have developed considerable experience conducting similar studies where rainbow and cutthroat trout were overdosed and overexposed to AQUI-S® (the 50% isoeugenol product that was removed from CVM review at the eleventh hour). In addition, CVM recently reduced (yes, that's right, reduced) the number of tissues that we need to collect and microscopically examine in each study based on data previously submitted to CVM. So, we're anticipating that the TAS studies should be relatively easy to conduct and write-up. But, we've grown accustom to the fact that very little is relatively easy in the world of aquatic species drug approvals, so we hope for the best and prepare for the worst.

Channel Catfish Pituitary Update:

Environmental Assessment woes: This past January the word came in from CVM's Environmental Safety Team (EST) that the amendment to the revised catfish pituitary Environmental Assessment (EA) that we had submitted on 1 December 2011 was not adequate to support a "finding of no significant impact" or FONSI. If CVM had issued a FONSI, the Environmental Safety technical section of the New Animal Drug Application (NADA) would have been considered complete, and no Environmental Impact Statement would have been required. So much for what we thought was low hanging fruit! CVM provided to us a detailed list of comments explaining the deficiencies that were not adequately addressed in the revised and amended EA. We will once again take up the EST suggestion that "it is highly recommended that the EST be contacted to discuss the required revisions prior to preparing and submitting the [newly] revised EA." The plan is to "get the band back together" and work with Roger Yant (sponsor; Hybrid Catfish Farm; Inverness, Mississippi USA) and Dr. Chris Green (Assistant Professor of Aquaculture;

Louisiana State University, Aquaculture Research Station; Baton Rouge, Louisiana USA) to address the currently identified deficiencies. Based on CVM's mandated six month review time for this type of submission, check AADAP's website and/or Newsletter near the end of the year to see if we get it right this time .

SLICE® (emamectin benzoate) Update:

SLICE® - Salmincola efficacy studies: In the last issue of the AADAP Newsletter, we reported that we had submitted FSRs to CVM summarizing three efficacy studies we had conducted to evaluate the effectiveness of SLICE® (sponsor; Merck Animal Health; Summit, New Jersey USA) administered in feed to reduce infestations of the ectoparasite *Salmincola californiensis* in female populations of rainbow trout. We also reported that Niccole Wandelear collaborated with Wesley Swee and the staff at the Missouri Department of Conservation's Maramec Spring Hatchery (St. James, Missouri USA) and had conducted a study of similar design on a mixed sex (i.e., boys and girls) population of rainbow trout. The Maramec Spring study met both the statistical and percent-reduction threshold criteria as outlined in the study protocol.

As it turns out, it was a darn good thing that we didn't bank too heavily on our belief that results from the first three studies would be sufficient to complete the Effectiveness technical section. In early September of last year, we received a disheartening letter from CVM. It stated that although they had accepted all three studies as part of "substantial evidence" of effectiveness, they could not provide to us an Effectiveness technical section complete letter for the use of SLICE® to control infestations of *S. californiensis* in rainbow trout. CVM provided the following reason: we did not adequately address the "…issue of the existence of any difference in the effectiveness of emamectin for *S. californiensis* between male and female fish." Notwithstanding the fact that we had provided information in a separate submission to CVM indicating that there is no significant difference in the body composition between male and female (specifically during non-spawning periods) and the depletion of emamectin in salmonids is similar regardless of gender and maturity of fish, CVM rejected our argument. We were informed by CVM that we had not provided sufficient information needed to determine that 1) fish gender has no significant effect of the intensity and distribution of the parasite on the fish, and 2) there is no difference in the effect of the drug at the site of action with respect to fish gender. Although there is most certainly nothing to suggest that age or gender will affect treatment efficacy, CVM is likely correct that we did not provide them with "hard and irrefutable data" to support the assumptions.

We will hear back next month whether the Maramec Spring SLICE® efficacy trial conducted on a male/female population of rainbow trout will be sufficient to complete the Effectiveness technical section. In spite of those occasions where our 'glass half full' outlook gets dumped over our collective heads, we are cautiously optimistic that this last study will be sufficient to address CVM's concern regarding differences (or lack thereof) of the effectiveness of SLICE® treatments to control or reduce infestations of *S. californiensis* in male and female rainbow trout, and thereby complete the Effectiveness technical section. As always, stay tuned.

SLICE® target animal safety study underway: Keeping our eye on the finish line (i.e., ultimate drug approval), we recently initiated a target animal safety study to evaluate the safety of administering SLICE® to small fingerling rainbow trout. Fish will be fed SLICE®-medicated feed at 0×, 1×, 2×, or 3× the proposed efficacious dose (50 µg emamectin benzoate per kg fish body weight per day) for 14 d (2× the proposed efficacious duration of 7 d). Fish were randomly allocated to test tanks (20 fish per tank) on 13 March 2012 where they will be allowed to acclimate for 7 d. SLICE®-medicated feed will be administered from March 20th through April 2nd. On April 3rd, all fish remaining alive in each tank will be necropsied and a select subset of tissues from 10 randomly selected fish from each tank will be processed for histological examination. Based on information in publically available reports and literature and from the folks at Merck Animal Health, we don't anticipate seeing anything to indicate that the SLICE® doses administered to the test fish will result in acute lesions or any lesions of biological concern. Completion of this study and CVM acceptance of the data will put us one step closer to the finish line.

FINS & TAILS, BITS & BOBBERS

Launch of the AADAP's INAD Program Management System: After much anticipation the INAD Program Management System (IPMS) – On-line Data Reporting database was officially launched on 8 February 2012….hooray!!

First things first, we would like to thank the many INAD participants who have stepped-up and quickly engaged in this brand new INAD data reporting process. To date, 253 individual user accounts have already been established (102 Study Monitor accounts and 151 facility accounts); 7 studies have been completed; and another 85 studies have been initiated and are in various stages (2-4) of completion.

All-in-all, we are happy to report that the IPMS appears to be running fairly smoothly. However, and certainly not unexpectedly, there have been a few "hiccups" reported with respect to data entry/data saving features

of the IPMS. Please rest assured that we are working on these issues, and hope to have them resolved very shortly.

As with any new program or database, there will obviously be a bit of a user learning curve with respect to becoming comfortable/proficient within the IPMS. To help facilitate this transition, we have prepared a step-wise IPMS User Manual that can be accessed at http://www.fws.gov/fisheries/aadap/IPMS/IPMS%20User%20Manual%208march2012.pdf. If you have **ANY** questions and/or concerns regarding the IPMS, please do not hesitate to contact Bonnie Johnson at 406-994-9905 or bonnie_johnson@fws.gov. Bonnie will be more than happy to "walk you through" your account, and answer any questions that you may have. Similarly, if you have any suggestions on how we can enhance/improve the functionality of the IPMS please don't hesitate to bend Bonnies' ear!

EDITORIAL

Regulatory Science, not Academic Science, Drives U.S. Aquaculture Drug Efficacy and Target Animal Safety Work

Dan Carty

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

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

Introduction and Objectives

A little over 10 years ago, we (AADAP) submitted a target animal safety research study protocol to the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) for review. We were confident the protocol would be accepted as written because we had worked closely with a university professor of biostatistics to ensure the study was biologically sound and statistically defensible. Moreover, data generated under the protocol would have allowed us to predict mortality over a wide range of exposure concentrations and durations. However, the protocol was not accepted as written, largely because CVM deemed the study would not have provided the specific biological information they needed to evaluate the safety of the drug to the target animals. After several rewrites and reviews, the protocol was finally accepted. However, the accepted version bore little resemblance to the original. A short time later, it was pointed out to me that AADAP was, in actuality, involved in regulatory science-based research not academic science-based research. I did not immediately understand the difference because—like most people—I had always assumed "science was science" and "research was research." However, when I did come to understand, it fundamentally changed the way I think about aquaculture drug efficacy and target animal safety work in relation to the U.S. aquaculture drug-approval process.

Much has changed during the past 10 years. What was mostly a teacher-student relationship between CVM and researchers has evolved into a more collaborative partnership. Moreover, presubmission discussions with CVM and a newly instituted, time-limited review process—including End Review Amendment requests—have helped minimize unpleasant surprises that are at times found in CVM's reviews of our protocols and final study reports (FSR). Unfortunately, miscommunication and misunderstanding still occur all too frequently, in part because many of us involved in aquaculture drug approval work might not fully understand or appreciate that the goals, objectives, and inferential values associated with regulatory science-based research are often very different from those typically associated with academic science-based research. Consequently, in this editorial, I describe important differences between these two sciences and approaches to research. My goal is to improve communication and understanding among sponsors, researchers, regulators, and end-users in ongoing efforts to obtain new or expanded claims for drugs needed by the U.S. aquaculture community.

Academic Science, Regulatory Science, and Research Defined

Science—derived from the Latin *scientia* (knowledge)—can be defined as the "...state of knowing, i.e., knowledge as distinguished from ignorance or misunderstanding..." (Mish 1984). The overarching goal of science is to expand our understanding of the natural world through an ongoing process of questioning, hypothesizing, validation, and refutation (CSTPR no date). Stated another way, the goals of science are to (1) organize knowledge in a systematic way while endeavoring to discover patterns of relationships among phenomena and processes; (2) provide explanations for the occurrence of events; and (3) propose explanatory hypotheses that are testable (Ayala 1968; Mayr 1982). Of course, these are the goals typically associated with *academic science*. In contrast to the open-endedness of academic science (CSTPR no date), *regulatory science* is narrowly focused. For example, FDA recently defined regulatory science as "...the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products..." (USDHHS 2010, 2011). Thus, the overarching goal of regulatory science is to

provide information needed to meet regulatory requirements and make regulatory decisions (CSTPR no date).

Research can be defined as a systematic and orderly process by which new knowledge is obtained in accordance with specific objectives (Waters and Erman 1990) and is conducted in an attempt to achieve the goals of academic or regulatory science. Wilm (1952) stratified research into three levels—exploratory/observational studies, controlled experience studies, and controlled experiments—in which the extent of human control over the experimental environment progressively increased. Hurlbert (1984) took a simpler approach, stratifying research into mensurative or manipulative experimentation. Mensurative experiments involve only the making of measurements at one or more points in space or time, where space or time is the only "treatment" variable. Manipulative experiments involve administering different treatments to different experimental units and randomly assigning treatments to experimental units. The controlled/manipulative type of experiment is typically associated with aquaculture drug efficacy and target animal safety work.

Academic Science-Based Research versus Regulatory Science-Based Research

Based on the definitions and goals provided for academic science, regulatory science, and research, it is evident that—even when controlled/manipulative experiments are conducted— academic science-based research is often not designed to provide the information CVM needs to make regulatory decisions about aquaculture drug efficacy and target animal safety and thus does not meet CVM's regulatory requirements. This is particularly true for those studies that need to be conducted under Good Clinical Practice (USDHHS 2001) or Good Laboratory Practice (USOFR 2011) guidelines. Also, CVM requires blinding (masking), dose verification, and submission of raw data for both efficacy and target animal safety studies and quality assurance inspections for target animal safety studies; however, these criteria are often not required for publishing research in peer-reviewed journals.

A second difference between the two approaches to research is how observed results are handled in a peer-reviewed journal article compared with an FSR submitted to CVM. In academic science-based research, uncertainty in observed results is embraced (CSTPR no date), comparisons with published work are expected (Day 1994), and both serve as the basis for discussion, making inferences, and proposing additional research. However, in efficacy and target animal safety FSRs, emphasis is placed on documenting that protocol requirements were met (i.e., that no "fatal" deviations occurred) and arguing for or against efficacy or target animal safety based solely on whether or not a null hypothesis was rejected (Carty 2011). Moreover, each FSR is typically evaluated on its own merit (Carty 2011) as opposed to being evaluated within the context of similar studies conducted under the auspices of either academic or regulatory science. Hence, in FSRs, it has been our experience that CVM does not require, and places little value on, comparing observed results with work published in peer-reviewed journals.

A third difference between academic science based-research and regulatory science-based research is the extent to which work published in peer-reviewed journals or reports/theses (i.e., gray literature) is valued and can be used in making decisions about efficacy and target animal safety within the New Animal Drug Application (NADA) process. In academic science, peer-reviewed literature is valued more highly than gray literature. The reason is that, in peer-review, experts evaluate a manuscript to help determine whether it meets a journal's standards for scientific rigor (DeVries et al. 2009), as well as the overall validity of assumptions stated and conclusions drawn. When a journal publishes a peer-reviewed manuscript, the information becomes readily available to other researchers and decision-makers. Researchers show respect for—but not necessarily concurrence with—peer-reviewed work by citing it as established knowledge, e.g., "Smith and Jones (2001) demonstrated that Drug A *is* efficacious when administered…" (Day 1992). Nevertheless, DeVries et al. (2009) noted that although peer review is essential to science, it is an imperfect process, and it has not been shown that papers published with peer review are generally superior to those without.

In the NADA process, both peer-reviewed literature and gray literature can be submitted to CVM in support of the approval of a candidate drug. Consequently, both types of literature are used in developing efficacy and target animal safety "white papers" (i.e., position papers), protocols, FSRs, and submissions of All Other Information (AOI; a required component of an NADA). It is our understanding that an AOI submitted to CVM should include all literature and reports related to the efficacy and target animal safety of a candidate drug. However, from our perspective, white papers have met with little success, and literature submitted under an AOI has been used to contradict results reported in FSRs but not to extrapolate the conclusions of an FSR to a broader claim of efficacy or target animal safety. Bell and Erdahl (2011) offered the opinion that, to date, neither peer-reviewed nor gray literature has contributed much to the effectiveness or safety documentation needed to obtain an approval. One potential bright spot

is that an *ad hoc* committee composed of sponsors, researchers, and at least one person from CVM has been asked to identify crucial elements that need to be incorporated in peer-reviewed or gray literature to be considered as part of the body of evidence necessary to support efficacy and target animal safety (Bell and Erdahl 2011).

A fourth and final difference between academic science based-research and regulatory science-based research appears to be the extent to which expert opinion is valued and can be used in making decisions about efficacy and target animal safety within the NADA process. We have noted that CVM has gained experience with, and confidence in, the advice of outside expert panels via the "Index Drug" process, which should allow them to reconsider the merits of expert opinion vis-à-vis the NADA approval process. There are many time-tested, structured decision-making techniques available (e.g., Coughlan and Armour 1992), and sponsors, researchers, and CVM should be able to agree on one or more techniques to incorporate expert opinion into the evaluation of efficacy- and target animal safety-related submissions. Surveys are another way to harness the power of expert opinion; however, proper survey design and testing are needed to minimize the potential for bias in the way questions are posed (Scheaffer et al. 1990; Pollock et al. 1994).

Conclusions

In this editorial, I have attempted to illustrate how regulatory science, not academic science, currently drives U.S. aquaculture drug efficacy and target animal safety work and have described important differences between regulatory science-based and academic science-based research. Some of the differences between these two approaches to science and research probably cannot be reconciled, but others probably can. Most important, I think more inferential value should be routinely placed on peer-reviewed literature and expert opinion when evaluating efficacy and target animal safety within the NADA review process. If CVM can work with sponsors, researchers, and end-users to accomplish this, it should greatly facilitate ongoing efforts to obtain new or expanded claims for drugs needed by the U.S. aquaculture community.

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RELEVANT LITERATURE

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

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

This list along with all the lists from previous issues of the AADAP Newsletter have been compiled in a master bibliography on the AADAP Website. It can be viewed or downloaded by clicking here.

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

Antibiotics and Bacteria

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Alves, E, et al. 2011. Photodynamic antimicrobial chemotherapy in aquaculture: Photoinactivation studies of *Vibrio fischeri*. *PloS One* **6(6):e20970**.

Arrojado, C, et al. 2011. Applicability of photodynamic antimicrobial chemotherapy as an alternative to inactivate fish pathogenic bacteria in aquaculture systems. *Photochemical & Photobiological* **10 (10):1691-1700**.

Cárcamo, JG, et al. 2011. Effect of emamectin benzoate on transcriptional expression of cytochromes P450 and the multidrug transporters (pgp and MRP1) in rainbow trout (*Oncorhynchus mykiss*) and the sea lice *Caligus rogercresseyi*. *Aquaculture* **321(3):207-215**.

Coppellotti, OO, et al. 2012. Porphyrin photosensitised processes in the prevention and treatment of water- and vector-borne diseases. *Current Medicinal Chemistry* **19(6):808-819**.

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Gopalakannan, A. and Arul, V. 2011. Inhibitory activity of probiotic *Enterococcus faecium* MC13 against *Aeromonas hydrophila* confers protection against hemorrhagic septicemia in common carp *Cyprinus carpio*. *Aquaculture International* **19(5):973-985**.

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Meinertz, JR, et al. 2011. Chronic toxicity of erythromycin thiocyanate to *Daphnia magna* in a flow-through, continuous exposure test system. *Bulletin of Environmental Contamination and Toxicology* **87(6):621-625**.

Mine, S, and Boopathy, R. 2011. Effect of organic acids on shrimp pathogen, *Vibrio harveyi*. *Current Microbiology* **63(1):1-7**.

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Noga, EJ, et al. 2011. Identification of histones as endogenous antibiotics in fish and quantification in rainbow trout (*Oncorhynchus mykiss*) skin and gill. *Fish Physiology and Biochemistry* **37(1):135-52**.

Paschoal, JAR, et al. 2012. Depletion study and estimation of the withdrawal period for oxytetracycline in tilapia cultured in Brazil. *Journal of Veterinary Pharmacology & Therapeutics* **35 (1):90-96**.

Pasharawipas, T, et al. 2011. Phage treatment of *Vibrio harveyi*: A general concept of protection against bacterial infection. *Research Journal of Microbiology* **6(6), 560-567**.

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Pridgeon, JW, et al. 2011. An in vitro screening method to evaluate chemicals as potential chemotherapeutants to control *Aeromonas hydrophila* infection in channel catfish. Journal of Applied Microbiology **111(1):114-124**.

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Roiha, IS, et al. 2011. Efficacy of florfenicol in the treatment of bacterial infections in halibut, *Hippoglossus hippoglossus* (L.), larvae. *Journal of Fish Diseases* **34(12):927-930**.

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USGS's CORNER

Sedatives: The Upper Midwest Environmental Sciences Center (UMESC) initiated a study to determine the exposure parameters (concentration and duration) that will maximize eugenol residues in the fillet tissue from rainbow trout exposed to AQUI-S® 20E (active ingredient eugenol) and determine the sample times that will adequately characterize the depletion of eugenol residues from the fillet tissue of exposed fish. Fish were exposed to 4 different concentrations of AQUI-S® 20E for 5 different durations. Data from this study will be applied to the impending eugenol total residue depletion study where fish will be exposed to ^{14}C-labeled AQUI-S® 20E. Maximizing eugenol residues in the fillet tissue will allow for an accurate characterization of depletion, distribution, and identification of eugenol residues in the fillet tissue. Contact Jeff Meinertz, jmeinertz@usgs.gov, for more information.

There are two processes use to determine the concentration of drug residues in the edible portion of an animal that are safe for human consumption. The Acceptable Daily Intake (ADI) is the process typically used to determine that concentration. The ADI, however, presumes chronic human exposure and thus determines the level that is safe for a person to consume every day for the rest of their life. Though well suited for some drug uses, the ADI calculation does not model well the potential for human exposure to residues of an immediate-release sedative used to sedate fish in fishery management operations. The second method used to calculate safe residue concentrations is referred to as the Acute Reference Dose (ARfD; similar to the Acceptable Single-Dose Intake concept). The ARfD process has typically been applied to model rare or bolus consumption events like the consumption of an injection site from a beef or pork carcass. The ARfD had not previously been applied in fish and FDA had no basis to accept that this calculation process was appropriate to model potential human consumption of fish recently sedated by an immediate-release sedative. To resolve this issue, UMESC submitted to USFDA's Center for Veterinary Medicine (CVM) a paper argument that justified that the ARfD calculation was an appropriate method to estimate the concentration of eugenol residues that is safe for occasional human consumption. CVM agreed with UMESC that the ARfD is the appropriate method to use when calculating the concentration of an immediate-release sedative that is considered safe for occasional human consumption. This is an important development in the process to attain an approval for eugenol as an immediate release sedative as the ARfD calculation more accurately describes the risk of human exposure to eugenol residues in recently sedated fish. Establishment of the safe concentration provides UMESC with a residue target for the conduct of tissue residue depletion studies to address the remaining human food safety technical section requirements. Contact Mark Gaikowski, mgaikowski@usgs.gov, for more information.

Florfenicol (active ingredient of AQUAFLOR®): UMESC conducted a study that fulfilled the following objectives: (1) determine the depletion rate of the florfenicol amine (FFA) residues from the fillet tissue of rainbow trout dosed with florfenicol (FFC)-medicated feed in a recirculating aquaculture system, (2) determine the FFC concentrations in the water of the recirculating aquaculture system during and after a dosing rainbow trout with FFC-medicated feed, (3) determine FFA residue concentrations in the fillet tissue of non-dosed rainbow trout sharing a recirculating aquaculture system with rainbow trout dosed with FFC-medicated feed, and (4) determine the depletion rate of FFA from the fillet tissue of rainbow trout dosed with FFC-medicated feed in a flow through aquaculture system. Analyses to determine FFC concentrations in the tanks were completed. Fillet tissue analyses are scheduled to be completed in April 2012. Contact Jeff Meinertz, jmeinertz@usgs.gov, for more information.

18th Annual USFWS Aquaculture Drug Approval Coordination Workshop: UMESC will host the annual USFWS Workshop in La Crosse, Wisconsin USA, 31 July 2012. The workshop will be held during the week when several other related meetings will be held in La Crosse including the Great lakes Fish Health Committee Meeting, the Veterinary Workshop on Fish Regulatory Medicine, and the 53rd annual American Fisheries Society Fish Health Section meeting. Information for each can be found through the following web site: http://www.uwlax.edu/conted/fish/index.htm.

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.

MEETINGS, ETC.

UPCOMING MEETINGS

Fish Immunology Workshop; 22-26 April 2012; Wageningen University; The Netherlands: The Wageningen fish immunology / vaccination workshops have been organized annually since 1998. Typically, the workshops are characterized by one-hour presentations given by experienced lecturers, taking time to thoroughly introduce each subject. This year's (2012) subject is FISH IMMUNOLOGY. The 2012 workshop includes two afternoons with a choice between hands-on practicals or updates on recent molecular advances in transcriptome analysis and gene synteny. Further, participants are asked to send an abstract of their research and be given the opportunity to bring a poster, with the best one awarded the poster prize. The official workshop language is English. For more information click here or contact the organizers at: fish.workshop@wur.nl.

37th Annual Eastern Fish Health Workshop; 23 - 27 April 2012; Lake Placid, New York USA: This year's Workshop, as in the past, is being organized by Dr. Rocco Cipriano of the U. S. Geological Survey's National Fish Health Research Laboratory in Kearneysville, West Virginia USA. The Workshop is being held at the High Peaks Resort and Conference Center in Lake Placid. The organizers are still accepting titles for the General Session, and already have 10 Special Sessions scheduled with a wealth of presentations in each. Additionally, a Continuing Education Opportunity is planned for the last day of the Workshop. For more information on the Workshop accommodations, registration, important dates, and

program content click here or contact Dr. Cipriano (rcipriano@usgs.gov).

Skretting Australasian Aquaculture 2012; 6-10 May 2012; Melbourne, Victoria Australia: The 2012 international conference is hosted by Asian Pacific Chapter of the World Aquaculture Society and the Australian National Aquaculture Council. The naming rights sponsor is Skretting, while the sponsors are Australia's Fisheries Research and Development Corporation and Melbourne Australia. The theme for this year's meeting is "The Next Ten Years" and in the words of the organizers "Whether it be genetic improvement of farmed species, advances in health management, increased production efficiency, or higher product quality for consumers - the aquaculture industry continues to develop innovative and sustainable practices" the theme is apropos. The conference *per se* will be held at the Melbourne Convention and Exhibition Centre, with several conference hotels close nearby. For additional information refer to the conference website.

Aquaculture UK 2012 Conference and Trade Exhibition: 23-24 May 2012; Aviemore, Scotland UK: This year's conference and exhibition is being held at the Macdonald Aviemore Highland Resort situated at the foot of the Cairngorm Mountains in the heart of the Cairngorms National Park. Details of conference sessions are scheduled to become available late in 2012, but are planned to fill two full days with a broad array of aquaculture topics. Detailed information, including registration, etc. can be found on the conference webpage at: http://www.aquacultureuk.com/index.php?c=home.

Aquaculture Canada^{OM} 2012; 27-30 May 2012; Charlottetown, Prince Edward Island Canada: This year's meeting is entitled *"New Frontiers: Bridging Technology and Economic Growth."* The meeting is being held in the PEI's capital city, Charlottetown. Planned sessions include the following: 1) integrated pest management; 2) reproductive containment of farmed fish; 3) coastal and marine spatial planning; 4) bio-economics: the real value of research; 5) advances in land-based aquaculture; 6) fish health (general); 7) genetics and selective breeding; 8) sustainability forum; 9) cultured shellfish forum; 10) advances in fish nutrition; 11) vet health global session; 12) the changing landscape of research and development; 13) environmental monitoring programs, new and emerging tools, latest research needs and objectives for marine finfish aquaculture; 14) shellfish carrying capacity; and 15) contributed papers. For more information refer to the conference website at: http://tinyurl.com/7mrnpso.

AQUAVET® I; 27 May - 23 June 2012; Bristol, Rhode Island USA: The course will be presented at Roger Williams University in Bristol, Rhode Island. Arrival and the start of classes is May 27th and departure is June 23rd. The fee for the 4-week course INCLUDES tuition and room and board. It is $1,975 for full-time veterinary students and $3,375 for veterinarians. Through the generosity of a program benefactor, a $200 scholarship will be applied to partially offset the fee for all full-time veterinary students resulting in a net tuition of $1,775 for the accepted full-time veterinary students this year. The program is diverse, incorporating many topics relating to aquatic organisms, their environment, and the application of traditional veterinary disciplines to aquatic animals. To deal with this breadth of subject matter, faculty members are enlisted from a variety of backgrounds and fields of interest, and a broad range of learning situations are used. In addition to lectures, laboratories, student seminars and discussions, there are field trips, practicums and films. Applications for admission are due by 14 January 2012. For more information, please refer to the AQUAVET® I web page: http://www.vet.cornell.edu/aquavet/one.cfm.

AQUAVET® II; 27 May - 9 June 2012; Bristol, Rhode Island USA: The course will be presented at Roger Williams University in Bristol, Rhode Island. Arrival and the start of classes is May 27th and departure is June 9th. The fee for the 2-week course INCLUDES tuition and room and board. It is $1,125 for full time veterinary students, and $1,850 for veterinarians. Applications for admission are due by 14 January 2012. AQUAVET® II is a natural extension of the AQUAVET® I. While similar in organization, the focus of AQUAVET® II is narrower, allowing a more detailed look at specific areas of aquatic animal medicine for students and veterinarians interested in continuing in the field. Recently AQUAVET® II has been presented as a two-week course on the pathology and histopathology of selected aquatic invertebrate and vertebrate species of importance as biomedical research models. Completion of the AQUAVET® I course, or adequate equivalent preparatory work is a prerequisite for admission to any AQUAVET® II course. In addition, it is generally assumed that applicants will have completed the basic science courses in the veterinary curriculum or have graduated prior to attending. For more information, please refer to the AQUAVET® II web page: http://www.vet.cornell.edu/aquavet/two.cfm.

East Coast Trout Management and Culture Workshop V; 11-13 June 2012; Frostburg, Maryland USA: The American Fisheries Society's Southern Division Trout Committee is hosting the fifth meeting focusing on trout on the east coast of North America. This year's meeting is entitled: *"Conservation and Management of East Coast Trout Resources in an Increasingly Crowded World"* and is being held on the campus of Frostburg State University. The organizers are encouraging presentation on the following topics: a) stream restoration for native and wild trout; b) assessing the value of long-term datasets (>10 years); c) aquatic nuisance species (ANS); d) living in the 21st Century; e) the three "R's" of Brook trout management: regulations, re-introduction, and restoration; f) 21st century genetics techniques and their practical application for todays fisheries managers; g) water quality threats to east coast wild trout resources; h) private land protection and the future of brook trout; i) tailwater trout management; j) coldwater culture for the future; biosecurity, disease, and aquatic nuisance species (ANS) threats to coldwater hatchery production; k) the role of coldwater hatcheries in native trout restoration and wild trout fishery establishment. For more information refer to the conference website at: http://www.sdafs.org/trout/ectmcw_v/second%20_call_for_papers_ECT_2012.pdf.

2012 Western Fish Disease Workshop; 13-14 June 2012; Boise, Idaho USA: The Idaho Department of Fish and Game is hosting the 53rd Western Fish Disease Workshop. The workshop is being held 13 and 14 June 2012 at The Grove Hotel, in Boise, Idaho. Registration and additional information will be available soon. The last day to obtain reduced hotel rates is 12 May 2012. 1 June 2012 is the deadline for abstract submission and 8 June 2012 is the last day for online registration. A continuing education session on "Fish Nutrition, Feeds and Feeding" is scheduled for 12 June 2012. For more detailed information refer to the actual second announcement by clicking here. Check on AADAP's website for new information as it becomes available.

Fish Health Meeting Extravaganza; 30 July through 3 August 2012; La Crosse, Wisconsin USA: In an effort to help most folks who are facing travel constraints, several fish health-related meetings are being held in conjunction with each other this year beginning the last week of July and ending 3 August.

- **Monday, 30 July:** The week starts out with an all-day ***Annual meeting of the Great Lakes Fish Health Committee*** (GLFHC).
- **Tuesday, 31 July:** Tuesday will prove to be an exceptionally busy day with three separate meetings taking place as well as an evening social.
  1. The second and final session of the aforementioned GLFHC meeting from 8:00 am to 12:00 noon.
  2. ***The Workshop for Veterinarians on Fish Regulatory Medicine.*** This all-day meeting is sponsored by the U.S. Department of Agriculture - Animal and Plant Health Inspection Service and the Wisconsin Department of Agriculture, Trade and Consumer Protection.
  3. The ***18th Annual U.S. Fish & Wildlife Service's Aquaculture Drug Approval Coordination Workshop***. This year's Workshop is being hosted by the U.S. Geological Survey's Upper Midwest Environmental Sciences Center. For more information on this refer to the following website http://www.uwlax.edu/conted/fish/index.htm or check on AADAP's Website.
  4. As a warm up to Wednesday's activities, and to complete an already rather busy day, the American Fisheries Society Fish Health Section (FHS) will hold a social/registration for its annual meeting scheduled to begin on Wednesday.
- **Wednesday & Thursday, 1 & 2 August:** The ***53rd Annual American Fisheries Society Fish Health Section*** (AFS-FHS) meeting (will begin Wednesday morning and extend through approximately 5:00 pm on Thursday 2 August.
- **Friday, 3 August:** The FHS has also scheduled a Continuing Education course for Friday 3 August.

The venue for all the meetings is the downtown Radisson Hotel in La Crosse. As other details become available for these meetings they will be posted on the AADAP website, as well as the conference website http://www.uwlax.edu/conted/fish/index.htm.

Health and Colony Management of Laboratory Fish; 3-17 August 2012; Bar Harbor, Maine USA: This course is offered at the Mount Desert Island Biological Laboratory, Salisbury Cove, Maine USA. Topics to be discussed will include general system design and water quality management, anatomy and histology of fish, general fish diseases and disease management strategies. Infectious and noninfectious diseases common to all fish as well as specific diseases of importance to laboratory-maintained zebrafish will be

discussed. The course will consist of lecture, laboratory exercises and discussions. During the course there will be an opportunity for students to discuss unusual and/or unsolved diagnostic case experiences from their home laboratories as problem-solving exercises. The course should be particularly valuable to technical staff, graduate students, postdoctoral fellows, junior faculty and investigators needing skills to monitor the health of a colony of aquatic organisms. The course also provides a unique educational opportunity for Residents in Laboratory Animal Medicine Programs. The deadline for application is 15 June 2012. For more information refer to the course website: http://tinyurl.com/28oamuo.

American Fisheries Society Special Symposium; 19-23 August 2012; Saint Paul, Minnesota USA: The symposium entitled "Understanding the Ecological and Social Constraints to Achieving Sustainable Fisheries Resource Policy and Management", is being planned to take place during the AFS 2012 meeting in Saint Paul, Minnesota, but as yet a specific date has not been set. The venue for the entire AFS annual meeting is the Saint Paul River Centre. The overarching goal of this symposium will be to discuss the factors that facilitate or hinder sustainable fisheries management, focusing on issues that cross disciplines and jurisdictional boundaries such as climate change, invasive species, and aquatic pathogens (such as Viral Hemorrhagic Septicemia virus , Infectious Salmon Anemia Virus, and others). Effective research, surveillance, and control strategies are critically important for aquatic pathogens, but given the nature of aquatic systems, coordinated research, enhancement/ restoration strategies, and management can be difficult to create, implement, and sustain. Although this broad symposium will include a range of topics, the American Fisheries Society's Fish Health and Fish Culture Sections are working together to develop the aquatic pathogens component of the program. Presentations and discussions will focus on how aquatic pathogens impact fisheries; hatchery design, operation, broodstock collection and fish stocking, and other fish culture activities; habitat and communities; and fisheries management, with the goal of identifying novel strategies to address the many 'moving parts' of managing aquatic pathogens in the environment. For more and current information, refer to the AFS webpage at: http://afs2012.org/.

9th International Conference on Recirculating Aquaculture; 24-26 August 2012; Roanoke, Virginia USA: The 2012 annual meeting is being sponsored by Aquacultural Engineering Society, Freshwater Institute, U.S. Department of Agriculture; Virginia Tech's College of Agriculture and Life Sciences, College of Engineering and Center for Organizational and Technological Advancement (COTA). The conference is being held at the Hotel Roanoke and Conference Center and includes sessions covering the following topics: algae culture, animal health and biosecurity, aquaponics, cool and cold water culture, commercial RAS case studies, economics, emerging species, hatchery, marine culture, nutrition and feeds, ornamentals, quality assurance, salmonid culture, shrimp culture, system design and engineering, warm water culture, and waste management. Additional information, including accommodations and registration can be found on the conference website: http://www.recircaqua.com/ icra.html.

Aqua 2012; 1-5 September 2012; Prague, Czech Republic: This conference, like that in 2006, is the combined meeting of the World Aquaculture Society and the European Aquaculture Society, with organizational assistance from the South Bohemian Research Center of Aquaculture and Biodiversity of Hydrocenoses; and the Faculty of Fisheries and Protection of Waters, University of South Bohemia České Budějovice. Numerous sessions and special sessions are being planned, as well after hour and tours. The conference theme is "*Global Aquaculture – Securing our Future".* For more information refer to the conference website at: http://tinyurl.com/3fgzads.

CVM's NOTES

Public Master File Website: A webpage for public master files is now available at: http://www.fda.gov/ AnimalVeterinary/DevelopmentApprovalProcess/ MinorUseMinorSpecies/ucm279384.htm. There are two lists of public master files on the webpage, those that have supported new animal drug approvals and those for drugs that are still in development. For public master files still in development, CVM has identified any technical section complete letters that are available under that file and posted them online. The purpose of this webpage is to recognize the work by public sponsors that has gone into current drug approvals for minor species and to provide another tool for collaboration between sponsors and stakeholders. CVM also hopes that by making this information readily available, current and future drug sponsors will be encouraged to pursue minor species approvals.

Text provided by Adrienne Kurtz; Aquaculture Drugs Team; Office of New Animal Drug Evaluation; Center for Veterinary Medicine, Food and Drug

Administration; Rockville, Maryland USA. Please contact Ms. Kurtz (Adrienne.Kurtz@fda.hhs.gov) if you have questions about Public Master Files.

MUMS Grants: As you most likely know, FDA has a grants program that was established by the Minor Use and Minor Species Animal Health Act of 2004 to support the development of new animal drugs intended for minor species (which includes all finfish and shellfish) and minor uses in major species. To be eligible, drugs must be designated through CVM's Office of Minor Use and Minor Species Animal Drug Development (OMUMS), and have a protocol for the proposed study that has been accepted by CVM's Office of New Animal Drug Evaluation. Our next open period for submission of grant applications will start on June 1, 2012, and close on July 20, 2012. Future open periods are listed at http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-10-001.html.

Text provided by Stuart Jeffrey; Office of Minor Use and Minor Species Animal Drug Development; Center for Veterinary Medicine, Food and Drug Administration; Rockville, Maryland USA. For further information on MUMS Grants, please contact Dr. Jeffrey (stuart.jeffrey@fda.hhs.gov or 240-276-8604).

Just a little diversion from the blah, blah, blah: Find, in the puzzle, all the words from the right-hand column, any of which can be horizontal, vertical, diagonal or spelled in reverse order. A prize will be awarded to the person who can find all the words the fastest.

National INAD Program

W	G	F	R	O	S	N	O	P	S	G	U	R	D	E
I	L	V	O	Q	T	H	L	Z	G	T	G	P	Z	M
R	H	Y	T	H	C	O	U	U	N	P	Q	P	Q	M
D	E	I	A	S	L	A	B	I	R	T	F	X	F	F
J	C	J	G	P	Q	U	A	X	H	D	D	G	I	A
C	I	T	I	A	M	N	U	X	T	D	N	S	Q	E
G	F	C	T	W	O	I	L	D	A	I	H	U	E	I
L	F	L	S	N	N	A	S	N	K	D	A	Y	N	E
A	O	L	E	I	I	L	I	R	I	C	I	O	T	F
R	P	K	V	N	T	B	A	S	U	S	I	A	I	D
E	A	X	N	G	O	M	E	L	T	T	V	T	K	A
D	D	I	I	V	R	A	T	A	A	I	J	Z	K	C
E	A	D	O	I	S	U	T	D	R	U	H	Z	D	V
F	A	X	V	E	R	E	E	P	X	M	L	P	O	M
W	I	N	R	E	H	S	O	Y	J	B	H	T	J	T

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