NATIONAL Aquaculture ASSOCIATION

Questions for Animal Health and Veterinary Industry

November 15, 2024

Thinking of the health needs on the horizon for the next 5 years for the selected sector, what would you describe as the strengths (what is working well) and the weaknesses (what isn't working well)? For example, are there sufficient prevention tools and treatments available for common diseases to support animal health and welfare? Are there sufficient professionals (e.g. veterinarians and accompanying staff) to provide services? Are there new technologies that will improve the way we approach animal health?

1. Strengths:

The U.S. public and private aquaculture community (~600 federal and state fish hatcheries and ~1,800 private fish farms) is active in every state and yields approximately 1.7 billion fish annually stocked for recreational fishing or to restore at-risk species, 1 billion freshwater bait fish, 633 million pounds of farmed seafood, and freshwater and marine ornamental fish aquarists and water gardeners value and enjoy enriching their lives.

The National Aquaculture Association[1] estimate approximately 700 to 800 species, varieties, and color-morphs of fish (farmed seafood, live recreational fish and bait, aquarium and water gardening ornamentals, fish for aquatic weed control), bivalve mollusks (clams, oysters, mussels, scallops), crustaceans (shrimp and prawn, crawfish), and reptiles (turtles, crocodilians) are being grown. Commercial aquaculture is estimated to sell $2.27 billion[2] annually and have a direct economic impact of $4 billion to rural inland and coastal communities.[3]

Production systems for aquatic animals include outdoor ponds and raceways, indoor and outdoor tanks or vats, coastal net pens and cages. Production systems for bivalve molluscs on submerged privately owned or state leased lands include direct planting to

[1] The National Aquaculture Association (NAA) is a U.S. producer-based, non-profit trade association founded in 1991 that supports the establishment of governmental programs that further the common interest of our membership, both as individual producers and as members of the aquaculture community. For over 33 years NAA has been the united voice of the domestic aquaculture sector committed to the continued growth of our industry, working with state and federal governments to create a business climate conducive to our success, and fostering cost-effective environmental stewardship and sustainability.

[2] 2022 Census of Agriculture, Table 2 (st99_1_002_002.pdf)

[3] Economic contribution of U.S. aquaculture farms - Kumar - Journal of the World Aquaculture Society - Wiley Online Library.

the benthos under netting or in net bags or contained on bottom, mid-water suspended or floating cages or suspended by “ropes” or lantern nets from surface rafts. Inherent strengths to U.S. aquaculture are the diversity of farmed aquatic animals, production systems, farm sizes and locations, and unique markets.

U.S. farmers cannot compete against the imported seafood tidal wave (6.9 billion pounds valued at $29.7 billion)[4] and must be innovative and flexible to identify and develop markets inaccessible to imports. An example being the production and sale of live aquatic animals or high-health early life stages to stock domestic and foreign farms for growout.

Aquatic animal health is critical to the production of high value, high quality live aquatic animals. Strengths that support aquatic animal health include:

Aquatic Animal Veterinarians

Although the number of truly knowledgeable, experienced aquaculture veterinarians is still far too small, more veterinary students and professionals are expressing interest in veterinary medicine for aquatic species. Recognizing the national dearth in knowledgeable veterinarians, in 1994 the American Veterinary Medicine Association created an Aquatic Veterinary Medicine Committee. The Committee organizes an aquatic animal session oriented to veterinarians at the AVMA annual conference and a veterinarian focused session during the only national aquaculture conference. The American Association of Fish Veterinarians is growing in numbers each year and offers a look-up service to find aquatic animal veterinarians and organizes a national conference to benefit their members.

An important strength for U.S. aquaculture is food animal veterinarians trained in the principles and employment of diagnostics for detecting pathogens and diseases within herds of animals. This is no different for fish. Whether a late night call for a suspect case or during a routine visit, veterinarians use their medical training and experience to manage and coordinate: identification and selection of the most appropriate fish to sample from pond, raceway, tank or net pen, and the appropriate number to sample for a given situation; the initial gross examination and assessment of those fish chosen; the selection and preparation of the most appropriate tissues to test and/or submit to an external lab; the most appropriate test(s) to employ given the initial clinical signs observed (e.g.: histopathology; culture and sensitivity; PCR; ELISA; IFAT; etc.); the interpretation of the laboratory results and application context of the situation; recommendation of best course of action; and follow-up including the further diagnostic tests and any treatment changes that may be warranted. The overall goal is to coordinate fish health management in the most efficient and cost-effective manner for the farmer and provide the timeliest service with the best and most expedient solution to minimize farm disruptions for the client.

[4] Fisheries of the United States, 2022

Flexible Drug Availability

"Extralabel use" is the use of a veterinary drug in a manner that is not in accordance with the approved labeling. Veterinarian may prescribe extra-label use of drugs to treat, for example, an animal or a disease that is not on the approved label. This flexibility is particularly essential for minor species, including fish, for which there are very few approved drug claims. However, extralabel use is prohibited by the Animal Medicinal Drug Use Clarification Act (AMDUCA) for any drugs applied in feed, including veterinary feed directive (VFD) drugs.[5] According to AMDUCA and the associated regulations, veterinarians cannot issue a VFD for anything other than what is on the approved label.

For example, Aquaflor® and Paqflor® (florfenicol)[6] is a VFD drug that is approved to control mortality in freshwater-reared salmonids due to furunculosis associated with *Aeromonas salmonicida*, and a veterinarian must issue a VFD accordingly. However, veterinarians are prohibited from issuing a VFD to treat the same disease if it occurs in saltwater-reared salmonids or in another species that is susceptible to the same disease. There are very few approved claims for VFD drugs for fish and they only address the most common diseases of commonly reared species.

There are more than 100 fish species of fish cultured in the USA for the seafood market. Most of which are not included within FDA approved therapeutic drug claims. Without extralabel flexibility, many fish would suffer and die unnecessarily from readily treatable diseases.

In December 2016, FDA issued a revised Compliance Policy Guide (CPG Sec 615.115), stating that "when there are no approved treatment options available and the health of animals is threatened, and suffering or death would result from failure to treat the affected animals, extralabel use of medicated feed may be considered for treatment of minor species" and "the Agency will not recommend or initiate enforcement action against the veterinarian, animal producer, feed mill, or other distributor when extralabel use is consistent with this document." Although it is non-binding and only reflects FDA's "current thinking", the Compliance Policy Guide for extralabel use of VFD drugs for minor species has allowed veterinarians room to operate and provided greater access to needed therapeutants for minor species, including fish.

LRP and DRS Drugs

In addition to the very limited number of approved drugs, there are two other categories of aquaculture drugs that may be used in the United States: Low Regulatory Priority (LRP) drugs and Deferred Regulatory Status (DRS) drugs. Both drug categories are described in the CVM Program Policy and Procedures Manual 1240.4200 Enforcement Priorities for Drug Use Aquaculture.

[5] Please visit this fact sheet for antibiotic and VFD information: Antibiotic Use in Finfish.

[6] FDA Approves First Generic Florfenicol for Controlling Mortality in Freshwater-reared Fish | FDA

Regarding LRP drugs, "The Agency is unlikely to object to the use of these substances" if they are used in accordance with the conditions identified in the Enforcement Priorities (e.g., they are used for the indications described and at the prescribed levels, etc.). The LRP includes 16 innocuous compounds that have applications in aquaculture, including ice (to reduce water temperatures and metabolic rates), salt (as an osmoregulatory aid), onion and garlic (for parasite treatments), and iodine (for egg disinfection).

The DRS category includes, "Products found not to be low regulatory priority but regulatory action deferred pending further study." There are currently only two DRS drugs: copper sulfate and potassium permanganate, both of which are used for the treatment of external infections/infestations of fish or their eggs.

The LRP- and DRS-related Enforcement Priorities have proven to be an important means of providing access to tools that do not warrant the same scrutiny associated with the process to register them as approved drugs. The FDA appears to take a dim view of the LRP and DRS lists and fails to recognize the potential of this mechanism to provide access to tools for fish health management. The LRP and DRS lists could be used in a manner consistent with the Veterinary Health Product (VHP) program launched by Health Canada to provide greater access to vitamins, minerals, traditional medicines, and so forth.

Drug Indexing

Indexing is an alternative to the traditional drug approval process established by the Minor Use-Minor Species (MUMS) Act for drugs that are used non-food producing minor species and non-food early life stages of food producing minor species. Despite the explicit mention of 'non-food life stages' in the MUMS Act and associated regulations, FDA CVM did not act on the opportunity to Index drugs until a 2019 article appeared in the World Aquaculture Society magazine entitled, *The Failure of MUMS and Aquaculture Indexing*. Subsequent conversation with the agency led to a joint effort by the author and the National Aquaculture Association to examine approved drug use by broodstock to demonstrate the unlikely appearance in the human food supply of treated broodstock and the complimentary regulations by other federal agencies that controlled the use and reporting of approved drugs (i.e., Clean Water Act discharge permitting). For fish, non-food life stages could now include eggs, fry, broodstock, or other life stages of food-producing species (defined by FDA as anything besides ornamental fish) that are not consumed by humans or used to produce animal feed.

The Agency has since withdrawn its Guidance for Industry on Indexing and has communicated that the guidance is being redeveloped to include non-food life stages of food-producing animals. Although very few products have been recognized as eligible for Indexing for use in non-food life stages of food-producing animals, it is encouraging to see the agency realigning its practices with both statute and regulation.

This diversity of interests and efforts has resulted in the United States being unique amongst nations in that a national natural resource management agency, U.S. Fish and

Wildlife Service, hosts a program focused on gaining approval and label claim expansion for aquatic animal therapeutants. Please see Aquatic Animal Drug Approval Partnership (AADAP) Program | U.S. Fish & Wildlife Service. Unfortunately, the Partnership is a shadow of its former self. Three federal programs once had numerous staff and line-item budgets dedicated to aquatic animal drug approval: the aforementioned AADAP Program, Harry K. Dupree Stuttgart National Aquaculture Research Center (SNARC) | USDA ARS and Upper Midwest Environmental Sciences Center (UMESC) | U.S. Geological Survey). The SNARC and UMESC programs are no longer funded by their agencies or actively involved in aquaculture drug approval activities.

While the U.S. Fish and Wildlife Service supports the Partnership, which is a strength, the dismantling of the interagency effort is sad proof the U.S. has a failed and fundamentally flawed therapeutant approval process which requires considerable time, effort and expense. The patience to invest public dollars only lasts so long. The Partnership is no longer the in-depth, "let's figure out how to get stuff done" effort it used to be. Those that have been involved in the drug approval effort for any significant amount of time as users, sponsors, or data-generating partners are frustrated and disheartened. And why is that? The last antibiotic approved for use in aquaculture was florfenicol in 2005 after 10 years and $12 million. Clearly FDA CVM has created a process that employes many but also one defending an approval process that cannot be supported by the size and scope of the aquatic animal drug market.

As a bright spot, the Partnership organizes, tracks and reports Investigational New Animal Drugs (INAD) studies. Investigational New Animal Drugs provide fish culturists, fish health biologists, and fishery managers with legal access to a broad variety of medications that are still in the approval process. While not intended to be an unrestricted point of access to aquatic animal drugs, the cost, studies and effort required by FDAC CVM approval have resulted in needed drugs languishing in the approval process and being accessible only through participation in an INAD study.

In 2024, the Partnership hosted their 30th annual Aquaculture Drug Approval Coordination Workshop where very frank conversations and presentations and a variety of questions are raised to move FDA-CVM towards reducing the time, effort and expense of approving therapeutants or extending the label claims for existing labels.

As outcomes of the annual workshop and Coalition pressure, FDA-CVM:

- Supports sending numerous staff members to attend and present during the annual workshop.
- Organizes and participates in quarterly virtual meetings with the Aquatic Drug Approval Coalition[7] to discuss questions and issues raised.

[7] As an example of the significant national interest to increase the number of approved therapeutants and the label claims for existing therapeutants, the Association of Fish and Wildlife Agencies (AFWA) created a Drug

- Actively accepts applications under the rubric of Indexing as provided in the Minor Use, Minor Species Act.
- Is creating an in-house therapeutant research program and is renovating an existing laboratory to conduct therapeutant research.

While these visible efforts are appreciated by the aquaculture community, they are not solving the lack of therapeutants and were developed within the severe constraints of the agency's intractable and damaging therapeutant paradigm which is fated to never change and is described next as the weakness.

2. Weaknesses:

Therapeutant Approval
FDA CVM applies a human drug approval process for aquatic animal health therapeutants. Due to the number of species involved in aquaculture, their rigidly adhered human drug approval paradigm and an agency adopted "one species, one rearing condition, one pathogen" approach it is more difficult, labor-intensive, and costly to get a drug approved for use in aquaculture than for any other food-producing animal. As a damaging outcome, the last antibiotic approved was in 2005 and cost ~$12 million over a 10-year period. Currently, three antibiotics are approved, and the limited choice creates antibiotic resistance.

Although the minor species status of fish provides for some incentives regarding funding availability and marketing exclusivity periods for approved products, these do not effectively address the poor return-on-investment calculation for aquaculture drugs approved for the US market. The markets are smaller than for major species, the investment needed to secure an approval is equal or greater than for major species, and the process is so onerous that for at least the last 25 years no major drug sponsors have been actively working to bring new therapeutants to market for aquaculture species.

The agency has resisted:

- Accepting therapeutants approved in countries of drug review and assessment capabilities and capacities similar to the United States.
- Creating a model fish for approval instead of testing individual species for approval.
- Accepting test data as being applicable to freshwater, brackish water and marine species.

Approval Working Group which hosts the Aquatic Drug Approval Coalition. The Coalition is co-chaired by AFWA and the National Aquaculture Association and composed of federal and state agencies, drug sponsors, researchers and extension specialists and farmers. The Coalition focuses on coordinating and communicating the broad scope of aquatic drugs challenges facing all disciplines in aquaculture. Its mission being "To Conserve and Enhance Fishery Resources and Aquaculture in North America by Promoting the Development and Use of Safe and Effective Drugs"

- Combining arbitrary categories of cold, cool and warmwater species that currently requires studies across all three categories to approve a therapeutant/extend a label claim.

The very high bar for approval does not reflect the relative importance or risk of an aquatic animal therapeutant of a quality required for humans versus the health care needs of farmed aquatic animals. The intractable and damaging paradigm for FDA-CVM is to only approve the perfect therapeutant. The effort to do so has created significant death and suffering for aquatic animals, increased production costs, lost productivity and increased importation of farmed seafood from far less careful or caring nations. Ironically, a different program within FDA tests less than 1% of imported seafood (6.9 billion pounds in 2022) for US prohibited therapeutants which are widely used in developing countries and frequently reported in imported farmed seafood.

Imported Seafood Drug Tolerance and Lack of Import Testing

Import Tolerances legalize the sale of imported products from food-producing animals containing residues of drugs that are not approved for use in the USA, so long as the residues fall below the established limits. Import Tolerances have been established for seven drugs used in aquaculture outside the USA, and two others are pending. Foreign producers can use these products and sell their fish to American consumers, but American fish farmers cannot access the same tools. In addition to creating an imbalance related to foreign competition, establishing Import Tolerances speaks to the widely accepted safety and efficacy of these drugs while preventing access to these tools in the USA because of supposed concerns regarding their safety and efficacy.

Issues regarding the development of approved drugs, and Import Tolerances are exacerbated by the limited surveillance and compliance activities that the FDA undertakes to stop the sale of illegal veterinary products and evaluate imported seafood for residues of unapproved drugs. The Government Accountability Office has examined the issue of drugs and foreign seafood repeatedly over the last 20+ years.

- Imported Seafood Safety: FDA Should Improve Monitoring of Its Warning Letter Process and Better Assess Its Effectiveness | U.S. GAO
- Imported Seafood Safety: Actions Needed to Improve FDA Oversight of Import Alert Removal Decisions | U.S. GAO
- Imported Seafood Safety: FDA and USDA Could Strengthen Efforts to Prevent Unsafe Drug Residues | U.S. GAO
- Seafood Safety: FDA Needs to Improve Oversight of Imported Seafood and Better Leverage Limited Resources | U.S. GAO
- Food Safety: Federal Oversight of Seafood Does Not Sufficiently Protect Consumers | U.S. GAO

The draconian nature of the drug approval process coupled with the lack of significant enforcement action against those that flout the rules disincentivizes those that want to do the right thing.

Agency Turf War Further Reduces Farmer Options
There is also considerable confusion regarding the definition of biocontrols/pesticides vs. animal drugs when it comes to aquatic species and which agency has regulatory authority regarding registration of such products. EPA recently approved the use of a peracetic acid-based product as a biocontrol in systems where fish are present; this approval was then rescinded following action by the FDA who claimed jurisdictional authority over the product as a drug. All this, for a product has widely published safety and efficacy data in fish and is already approved by both agencies for applications involving direct contact with food (i.e., as a peeling aid or in wash water for fruits and vegetables) or cleaning of food-contact equipment and surface and aquaculture rearing systems (e.g., recirculation aquaculture systems and ponds). Greater streamlining and harmonization between the agencies would seem prudent given these outcomes.

3. What do you see as the biggest threat to animal health in the selected sector, and why?

Loss of the Consent of the Governed
The time, cost and effort to approve therapeutants according to the FDA-CVM framework coupled with the meager 'success' of only three approved antibiotics crossing the finish line in decades has eroded the fundamental premise of governance in the United States: Consent of the governed. As an example, unlabeled antibiotics are widely available in the marketplace even though FDA has acted in a very public manner to stop sales and distribution: FDA Warns Nine Manufacturers, Distributors of Unapproved Antimicrobials for Animals | FDA. Current examples being:

- Kanamycin Sulfate | ChuChuGoldfish
- Enrofloxacin (Baytril) Discus Medication - Jack Wattley Discus
- Praziquantel Powder – Discus.com
- KORDON Malachite Green Fish Disease Control Aquarium Treatment, 4-fl oz bottle - Chewy.com
- Aqua-Mox Forte 500 mg - Pet Supplies online store (amoxicillin)

Agency intransigence to act in a timely manner and at a cost to drug sponsors and the taxpayer that is sensible for the aquaculture marketplace has triggered and will trigger businesses to market illegal products in response to strong customer demand to provide aquatic animal health care. The availability of therapeutants from an easily accessed global marketplace has created a perception FDA is an insensitive, ineffective, tunnel visioned, and an out-of-touch with reality federal bureaucracy.

The World Does Not Stand Still for FDA
Despite oversight by USDA APHIS and numerous state-level regulatory authorities, domestic and international movement of live animals has the potential to contribute to the spread of pathogens. Additionally, the ranges of established pathogens and the risk of clinical disease are likely to be greater in the future as a result of climate change. Recent experiences (e.g., outbreaks of vagococcal infections in salmonids, tilapia lake virus, virulent *Aeromonas hydrophila*, ostreid herpesvirus-1) have shown that the United States is ill-equipped and fatally crippled to address these new or emerging threats to aquatic animal or ecosystem health. Additional therapeutants are needed, but any given therapeutic product will be decades and tens of millions of dollars away from becoming an approved aquaculture drug in the current framework.

4. What do you see as the biggest opportunities in the selected sector, and why?
Exciting Technologies

New vaccine platforms and delivering systems, gene silencing technologies, and the use of natural products (e.g., essential oils and other phytocompounds) and bacteriophages as therapeutic or biocontrol agents are all exciting developments in the aquaculture sector. Unfortunately, for all but the vaccines (that are regulated by the USDA Center for Veterinary Biologics, not FDA-CVM), there is no established pathway for securing the necessary approvals and making such products available.

Foreign – United States Equivalency
Nutritionist recommend Americans consume two seafood servings a week to benefit from:

1. Omega-3 Fatty Acids: Essential for heart and brain health.
2. High-Quality Protein: An essential building block for a healthy body.
3. Essential Vitamins: Boosts the immune system and more.
4. Vital Minerals: Supports thyroid health and other bodily functions.
5. Longevity: Reduces the risk of premature death.

Only 10 to 20% of Americans meet or exceed this advice. If the cost of farmed seafood production could be reduced, currently aquatic animal health regulation contributes to ~7% of production costs, and imported seafood was required to meet the same U.S. standards for therapeutant use, environmental protection and conservation, and labor protections, then the current societal trend to eat local, eat healthy could be satisfied by U.S. farmed seafood.

FDA-CVM should be directed to recognize and support the benefits of U.S. farmed seafood to Americans that could be gained versus their tunnel vision focus on the perfect therapeutant.

Focusing on the animal food/feed supply (i.e., the animal feed or pet food) for the selected sector and thinking within a time frame of the next 3 to 5 years, what do you see as the strengths (what is working well) and the weaknesses (what could be improved)? For example, you might consider the safety, quality and availability of animal food/feed, or the efficiency of feed conversion into animal growth sustainability of food/feed ingredients and animal production.

5. Strengths

Agricultural Productivity
The United States has one of the largest 'bread baskets' and terrestrial livestock production sectors in the world. The U.S. farmer and rancher is producing more food with less land and fewer inputs (quantity or number) in any time in world history.[8] U.S. agriculture is able to economically produce massive volumes of agricultural products/byproducts that serve as raw materials for the production of animal feeds, including those direct and derivative ingredients for fish feed.

Innovation
Compounded feed manufacturers and feed ingredient manufacturers are adopting or providing substitutes for wild harvested forage fish meal and oil (microbial, insect, plant, or marine macrophyte sourced products) to meet societal sustainability demands and to reduce final product cost (feed composes 50 to 60% of fish farm input costs).[9]

6. Weaknesses

FDA Approval
For the past 17 years, the Association of American Feed Control Officials (AAFCO) has provided scientific support to the FDA for the definition of animal feed ingredients. Last month, the long-standing Memorandum of Understanding between the two organizations expired, ending what had been a relatively straightforward and predictable process for ingredient suppliers to bring new products to the market. While the FDA has issued a Request for Comments and draft guidance documents about the feed ingredient definition process going forward (Draft GFI #293 and #294), nothing has been resolved and it is not clear how this process will work going forward.

Similar to the drug approval process, many feed ingredients are defined for terrestrial species but not explicitly defined for applications in aquaculture feed (e.g., calcium formate is approved for use as an acidifying agent for swine and poultry feed). As noted

[8] The level of U.S. farm output in 2021 was 190 percent more than in 1948, growing at an average annual rate of 1.46 percent. Over 1948–2021, aggregate input use decreased by -2 percent overall, at a rate of -0.03 percent annually, so the growth in farm sector output was entirely attributed to total factor productivity growth, which increased at an annual average rate of 1.49 percent over the full period. USDA ERS - Summary of Recent Findings.
[9] NOAA USDA Alternative Feeds Initiative | NOAA Fisheries.

above, this is a limitation that unduly constrains manufacturers that produce feed for aquatic species and limits the application of novel nutritional approaches primarily to terrestrial species.

Any commercial interest in developing ingredients that inhibit microbial contamination is stymied by an approval process complicated by FDA oversight. The recent agency decision making to move ingredient approval to their insular domain points to increased cost, time and effort to approve ingredients.

An examination and critical analysis should be completed by an objective third party as to why the memorandum of understanding between FDA and the American Feed Control Officials was abandoned. Are there any benefits or efficiencies gained from no longer partnering with the states on this issue?

7. What observations, if any, do you have about the manufacturing and supply chain for the food/feed supply in the selected sector?
Supply Chain Risk

Feed is a just-in-time manufactured and delivered product of limited shelf life. U.S. port and rail labor issues have disrupted and are constraining the transport of feed and feed ingredients. If rail transportation is disrupted, farms may exhaust their feed supply within 14 days.