



# **U.S. FDA Regulation of Aquaculture Drugs**

Lisa Weddig  
National Fisheries Institute



# Who is NFI?



- Leading advocacy organization in the U.S. for the seafood industry.
- NFI's members represent every element of the industry
  - fishing vessels
  - processors
  - importers
  - restaurant and retail chains
  - suppliers to the industry
- NFI and members support and promote sound public policy based on science.



# Agenda



- Why antibiotics in aquaculture seafood a concern for U.S. Importers
- U.S. FDA Regulations for the use of aquaculture drugs
- U.S. FDA regulatory compliance and inspection programs
- Questions about product testing
- HACCP Controls for aquaculture drugs
- Challenges (discussion with all)
- Questions and Answers



# **Antibiotics**

Why a concern?



# Top Ten Species - 2013

Shrimp	3.60	Pangasius	0.771
Salmon	2.702	Cod	0.605
Canned Tuna	2.30	Catfish	0.566
Tilapia	1.43	Crab	0.548
Pollock	1.154	Clams	0.352

U.S. Per capita consumption is 14.5 pounds  
(less than 4.5 ounces per week)

*Source: National Fisheries Institute at [www.aboutseafood.com](http://www.aboutseafood.com)*



# Encouraged to Eat More



- *2010 Dietary Guidelines for Americans* ([www.dietaryguidelines.gov](http://www.dietaryguidelines.gov))
  - Twice a week make seafood the main protein food on your plate.
  - Eating about 8 ounces per week of a variety of seafood can help prevent heart disease

**10  
tips**

*Nutrition  
Education Series*

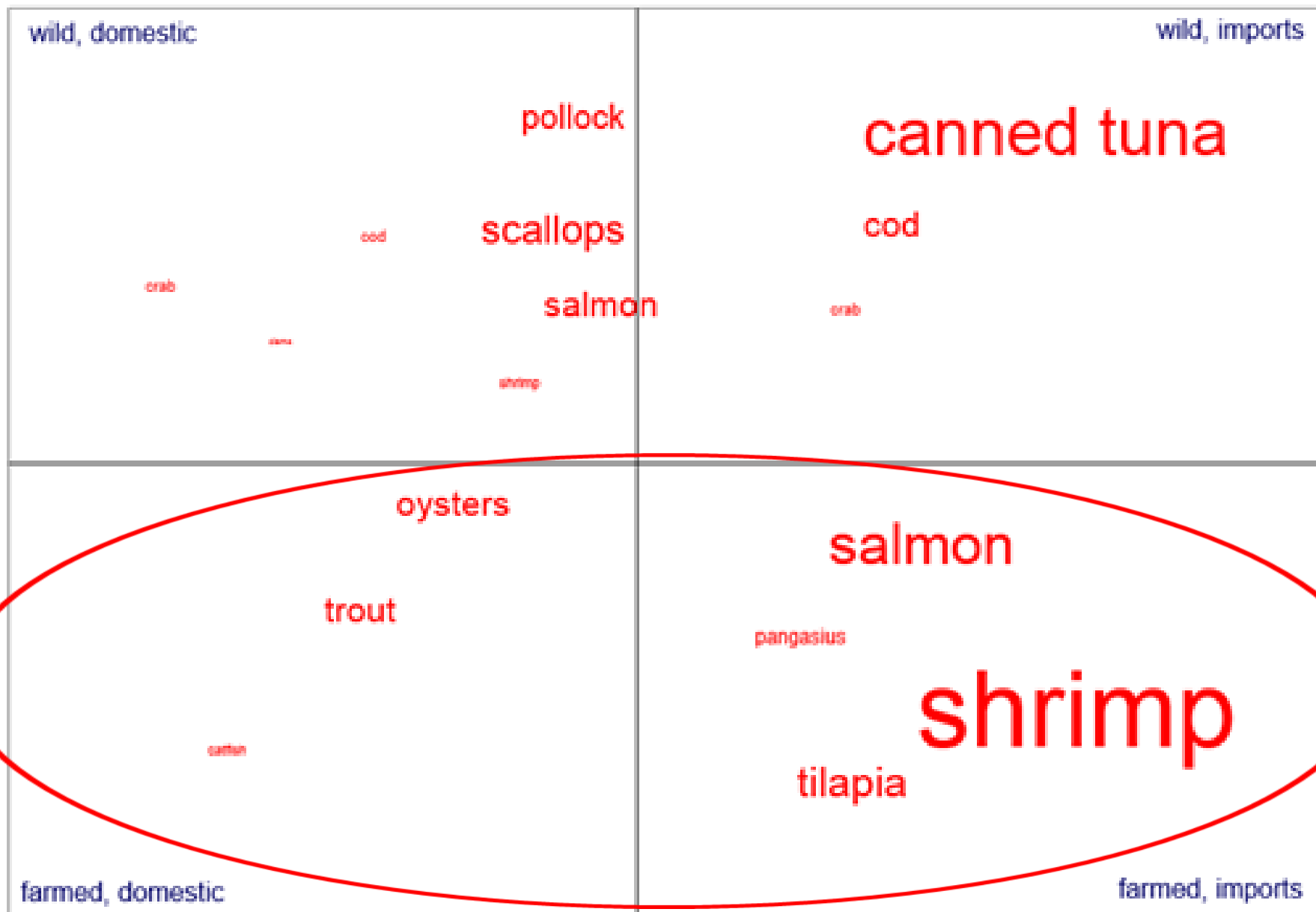
**eat seafood  
twice a week**

**10 tips** to help you eat more seafood

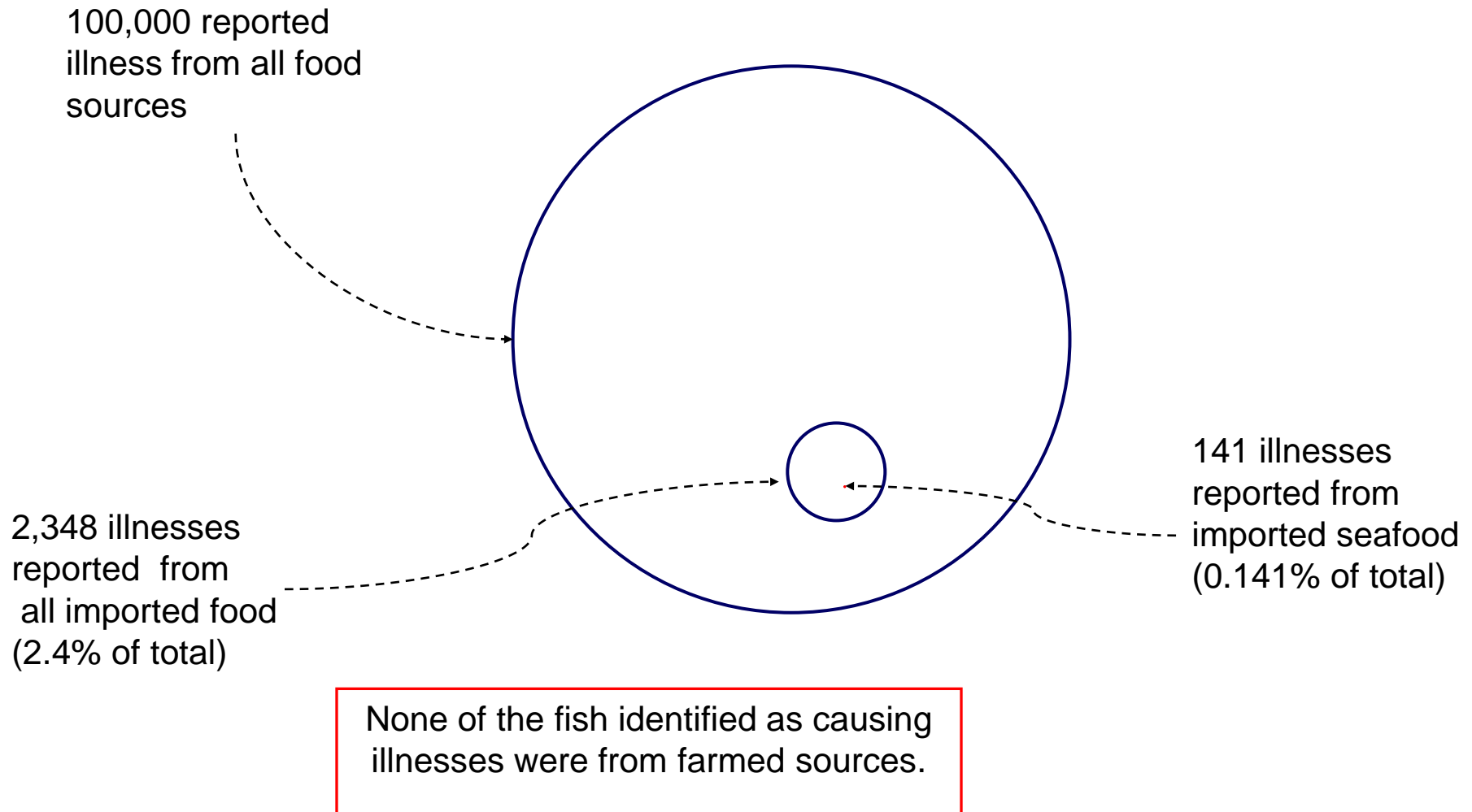




# Source of Seafood



# Center For Disease Control Analysis of Reported Illnesses from Food 2005-2010







Congresswoman

**ROSA DELAURO**



Representing the Third District of Connecticut

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## **Bipartisan Group Presses For Consumer Protections In Trade Negotiations**

Trans-Pacific Partnership Could Open U.S. To Contaminated Seafood

WASHINGTON, DC—Congresswoman Rosa DeLauro (D-CT), Senator Mary Landrieu (D-LA) and Congressman Walter Jones (R-N.C.) pressed the Obama Administration today to ensure public health is protected as they continue to negotiate the Trans-Pacific Partnership (TPP) Free Trade Agreement. As a result of expanded trade with two particular TPP countries, Vietnam and Malaysia, the United States markets could see an influx of imported contaminated seafood. In a letter to US Trade Representative Ron Kirk, the members urged him to pursue agreements with these two countries to help ensure the American food supply is kept safe.

"In Fiscal Year 2012, imported seafood products from Vietnam, the fifth largest exporter of shrimp to the United States, were refused entry 206 times because of concerns including filth, decomposition, drug residues, unapproved food additives and *Salmonella*. "Meanwhile... U.S. Customs and Border Protection (CBP) and Immigration and Customs Enforcement (ICE) officials determined that some exporters in Malaysia have acted as conduits to transship Chinese shrimp to the United States in order to circumvent both FDA Import Alerts and antidumping duties," they wrote. "We strongly believe that these critical food safety issues should be resolved prior to the conclusion of the TPP FTA negotiations in order to best protect the public health from these known health risks."



Congresswoman

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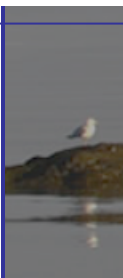
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## The Catfish Institute News Alert

### *Public Interest Group and Congresswoman Cite Asian Seafood Safety "Problem"*

June 2, 2015 -- As Congress continues debating the Pacific Rim free-trade agreement known as the Trans-Pacific Partnership, seafood safety experts say the free-trade agreement could reduce the safety of food imports. "Consumers deserve to know how the Trans-Pacific Partnership (TPP) could affect the safety of the food they feed their families," declared Patrick Woodall, Research Director and Senior Policy Advocate of the non-profit, non-partisan Food & Water Watch. The seafood safety [organization commended](#) U.S. House Members Rosa DeLauro, Louise Slaughter and Chellie Pingree for demanding public release of import safety provisions of TPP, the controversial Pacific Rim free-trade agreement that could override U.S. law.

Congresswoman [Rosa DeLauro stated](#), "...the TPP will limit our ability to stem the tide of harmful products, particularly seafood from Vietnam and Malaysia."

Citing seafood from Vietnam and Malaysia, [Mr. Woodall said](#), "We know there is a problem with these imports." Mr. Woodall went on to say that fish farmers in the TPP partner nations of Vietnam and Malaysia often use veterinary medicines and fungicides that are illegal in the United States to combat disease in overcrowded fish ponds and river cages.





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# 7 Foods Nutritionists Won't Eat

by [Toby Amidor](#) in [Healthy Tips](#), August 5, 2015



PRINT



## Imported Farm-Raised Shrimp

"I make a conscious effort to purchase and consume sustainable seafood, for both environmental and personal health. Imported shrimp are often unsustainably farmed and laden with chemicals and antibiotics. Sticking to this can certainly be a challenge, since 94 percent of the shrimp we consume in the U.S. is imported!"

—[Kristy Del Coro](#), M.S., R.D., CDN, senior culinary nutritionist at SPE Certified



"While US fisheries are very strictly managed, I am not confident that the same level of management is upheld for global fisheries."

"While there are certainly standards in place as you pointed out, to my knowledge they are not necessarily enforced. For example, while not allowed in the US, shrimp in many foreign farms are given daily doses of antibiotics which we know can lead to antibiotic resistant disease."

"... over 90% of the shrimp in the US is imported and less than 2% is inspected by the FDA is sufficient reason for me to personally avoid consuming this particular type of seafood ..."



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# SAFE CATFISH .COM

## Imported Catfish

### Dangers of Unregulated, Imported Catfish

Imported catfish may be contaminated with antibiotic, pesticide or bacterial residues. Imported catfish often come from Southeast Asia, where use of chemicals and antibiotics is barely regulated. Because the U.S. Food and Drug Administration inspects less than 2% of imported seafood, imported catfish may be contaminated with antibiotic, pesticide or bacterial residues.

**MORE INFO:**







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[Southern Shrimp Alliance](#)

## August Sets New Record for FDA Refusals of Shrimp Entry Lines Based on Antibiotic Contamination

September 4th, 2015

The U.S. Food and Drug Administration (FDA) today released to the public information regarding entry line refusals for the month of August. The agency reported refusing a total of 207 seafood entry lines last month. Of these, **72** (35%) were of shrimp entry lines refused for reasons related to banned antibiotics.

The refusals of 72 separate entry lines of shrimp for reasons related to antibiotics is the highest amount reported by FDA for any month going back to 2002. With fourteen years worth of data available through the agency's website, the top five months for shrimp entry line refusals have occurred during the first eight months of this year:

Rank	Month	Shrimp Entry Line Refusals for Antibiotics
1	August 2015	72
2	March 2015	58
3	January 2015	58
4	July 2015	54
5	April 2015	51

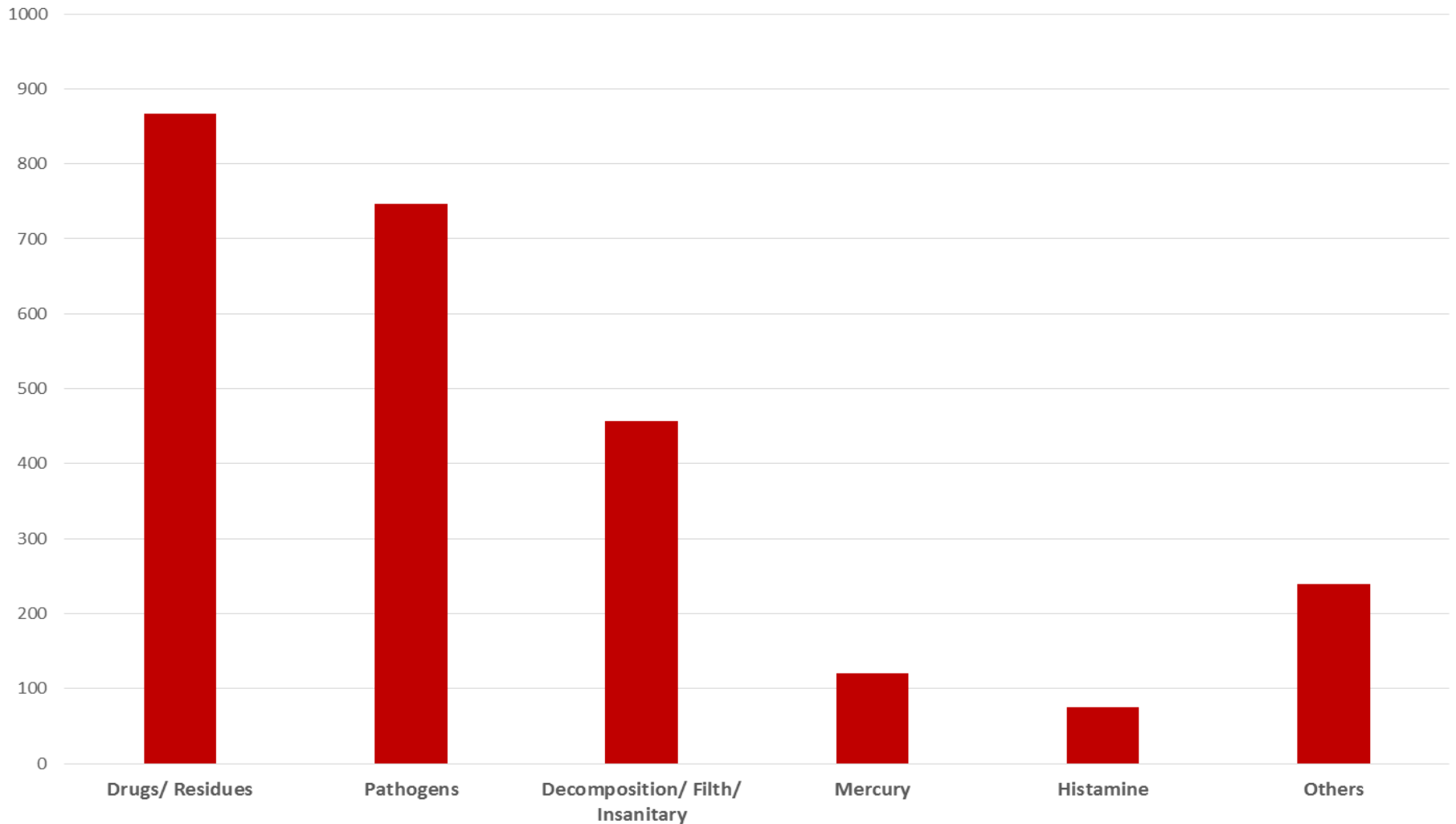
Through last month, the FDA has now refused a total of **358** entry lines of shrimp products for reasons related to banned antibiotics. This exceeds the total amount of entry lines of shrimp refused by the FDA for the same reasons over the three

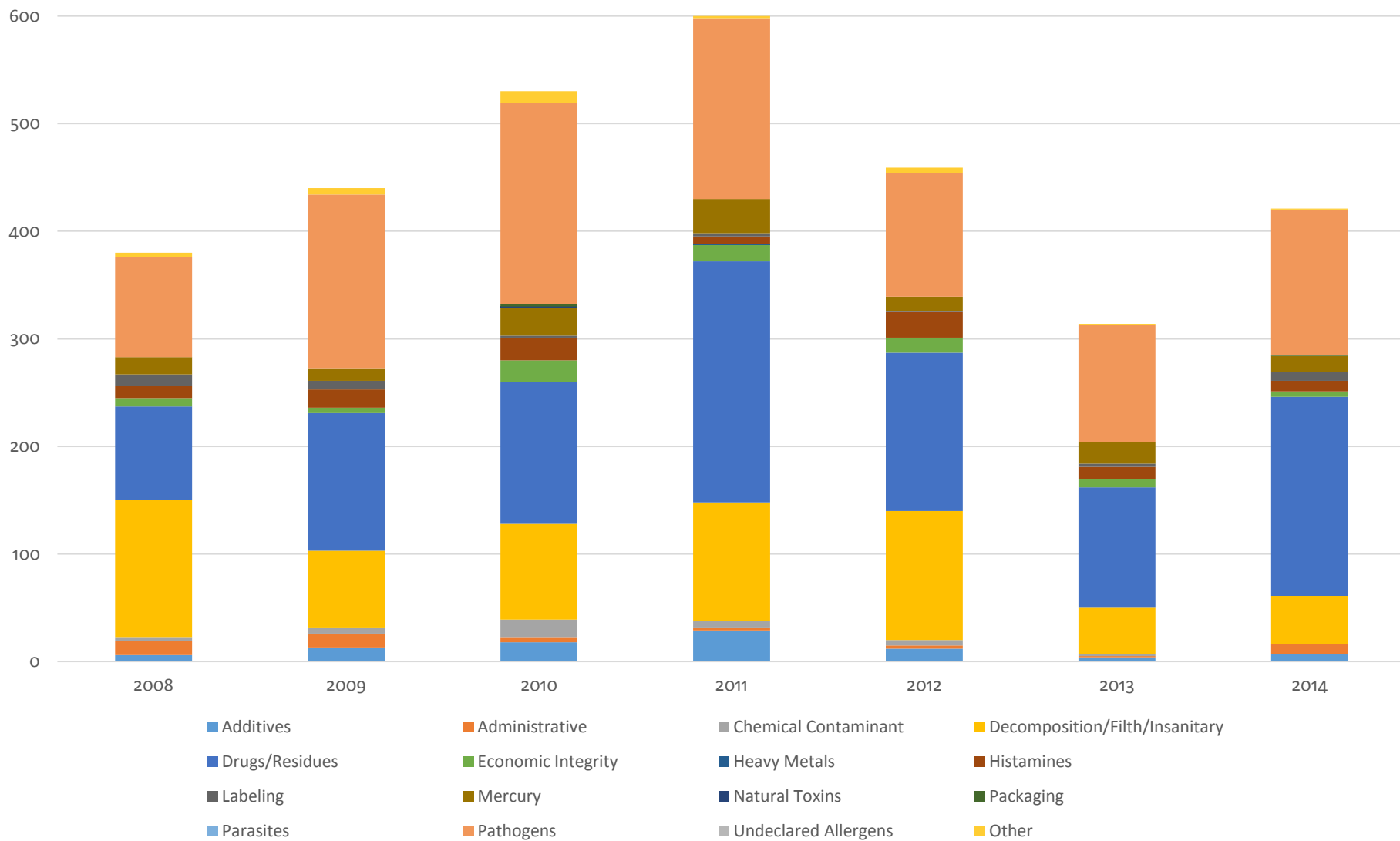


# Why a Concern?



**Refusals of Seafood Products from Vietnam  
by Australia, Canada, EU, Japan and the United States  
January 2010 - June 2014**



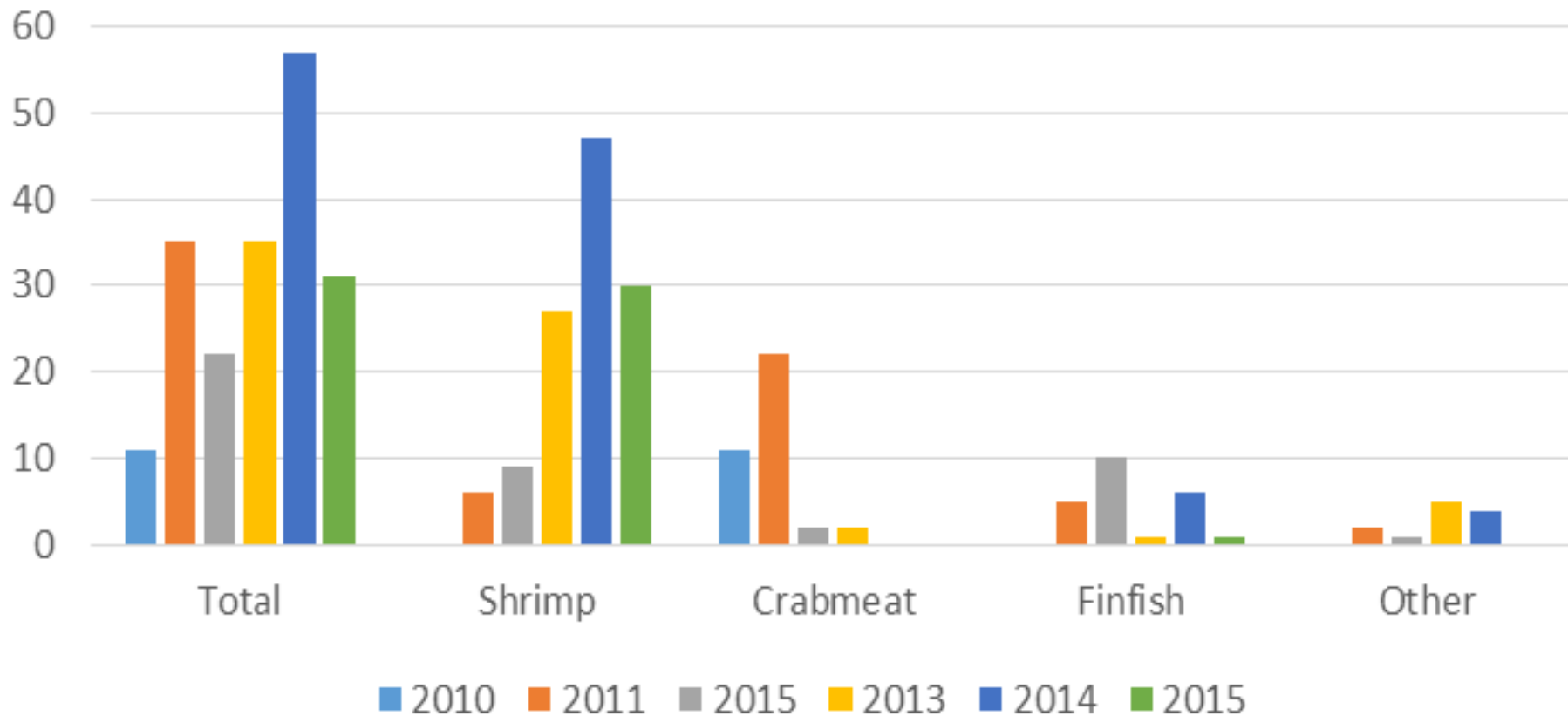




# Why a Concern?



Refusals of Seafood Products from Vietnam  
by the U.S. FDA for Illegal Drug Residues  
January 2010 - July 2015





# 2014 Findings

- Australia
  - Ciprofloxacin
  - Enrofloxacin
  - Furazolidone
  - Leuco-Malachite Green
  - Malachite Green
  - Nitrofurazone



# 2014 Findings

- European Union

- chlorpyrifos
- trifluralin
- doxycycline
- chloramphenicol
- nitrofurantoin (metabolite) furazolidone (AOZ)
- nitrofurantoin (metabolite) nitrofurazone (SEM)
- doxycycline
- oxytetracycline
- sulfadiazine
- sulfonamide
- tetracycline
- trimethoprim
- ciprofloxacin
- oxytetracycline
- sulfonamide
- trimethoprim
- leucomalachite green
- malachite green
- permethrin



# 2014 Findings

- Canada
  - AMPHENICOLS
  - AVERMECTINS
  - FLUOROQUINOLONES
  - NITROFURANS
  - QUINOLONES
  - SULFONAMIDES
  - TETRACYCLINES
  - TRIPHENYLMETHANE  
DYES (MG & GENTIAN  
VIOLET)



# 2014 Findings

- Japan

- paclobutrazol
- chlorpyrifos
- prometryn
- chloramphenicol
- chlortetracycline
- dieldrin
- enrofloxacin
- furazolidone (as AOZ)
- furazolidone
- Leucomalachite green
- oxytetracycline
- sulfamethoxazole
- aldrin
- chlordane





# FDA Regulations





# Scope of CVM



- Center for Veterinary Medicine (CVM) protects both animal health and human health
- FDA-CVM regulates:
  - Animal Drugs
  - Animal Feed (which includes pet food)
  - Veterinary Devices
- FDA-CVM does not regulate:
  - the practice of veterinary medicine
  - vaccines for animals.



# CVM Activities



- New Animal Drug Review
- Animal Generic Drug Review
- Post-approval monitoring (surveillance) of animal drugs.
- Protection and Safety of Animal Feed
- Compliance actions
- Research to support regulatory decision-making



# FDA Approved Aquaculture Drugs

Drug	Approved Species
Chorionic gonadotropin	Brood finfish
Formalin	Finfish Finfish eggs Penaeid shrimp Salmon, trout, catfish, largemouth bass and bluegill
Florfenicol	Channel catfish salmonids
Tricaine methanesulfonate	Families: Ictaluridae, Salmonidae, Esocidae and Percidae
Oxytetracycline dihydrate	Catfish, salmonids, lobster
Oxytetracycline hydrochloride	Finfish fry and fingerlings
Hydrogen peroxide	Fishfish eggs Salmonids Freshwater-reared coolwater finfish Channel catfish
Sulfamerazine	Trout (rainbow, brook, brown)
Sulfadimethoxine/ormetoprim	Catfish Salmonids (trout and salmon)
Chloramine-T	freshwater-reared salmonids walleye, freshwater-reared warm water finfish



# Aquaculture Drugs and The Food and Drug Administration



## What is FDA's role?

The Food and Drug Administration (FDA), and more specifically FDA's Center for Veterinary Medicine (CVM), is responsible for protecting public and animal health by assuring the safety, effectiveness, and security of animal drugs and feeds. Our legal mandate comes primarily from the Federal Food, Drug, and Cosmetic Act (FFDCA) and its amendments. In addition, there are other laws that influence what we do, such as the National Environmental Protection Act, which, for example, ensures that we assess a drug's impact on the environment before we approve the drug.

What is considered a drug? The FFDCA defines "drugs" as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."

Note that the U.S. Department of Agriculture, not FDA, regulates vaccines for animals and the Environmental Protection Agency oversees pesticides (weed treatments, etc.)

## The Drug Approval Process

For a drug approval, CVM evaluates information on the following:

- Effectiveness
- Target Animal Safety
- Human Food Safety
- Environmental Impact
- Chemistry, Manufacture
- All Other Information
- Labeling



**The benefit to you:** Not only have tests been done on the safety and effectiveness of the approved drug, but the drug company must manufacture the approved product to strict standards to ensure that you get the same product consistently. So, besides it being the legal thing to do, you know that the approved product is the smart choice anyway.

*Did you know?* A lot of work goes into a drug approval and work is being done by various public partners to increase the number of approved drugs to treat fish. Additionally, FDA, through the Minor Use and Minor Species Act, is able to provide financial incentives for the development of drugs for fish.

*Did you know?* After a drug is approved, CVM makes public a Freedom of Information Summary which describes the information that was evaluated. If an Environmental Assessment was prepared, it will also be available. The documents are helpful for those looking to view data on the safety and effectiveness of the drug.

## What's Legal to Use?

### FDA-Approved Drugs

Look for a six digit new animal drug application (NADA) number on the label.

Currently the following have approved aquaculture uses: (\* means that a veterinarian is required because the drug is prescription only or a Veterinary Feed Directive drug)

AQUAFLO<sup>®</sup>  
ROMET-30  
TERRAMYCIN 200 for FISH  
CHORULON<sup>®</sup>  
FORAMCIDE-B, FORMALIN-F, PARACIDE-F, PARASITE-X  
35% PEROX-AID  
OXYMARINE, Oxytetracycline HCl Soluble Powder-343,  
PENNOX 343, TERRAMYCIN 343, TETROXY AQUATIC  
FINQUEL, TRICAINE-S

### FDA-Conditionally Approved Drugs

Conditional approval means that the drug has been demonstrated to be safe and the drug can be marketed for up to five years while all the effectiveness tests are completed.  
The following drug has a conditional approval: AQUAFLO-CA1<sup>®</sup>

### FDA-Indexed Drugs

Indexing is available for only some fish drugs: those for non-food fish, or for early, non-food life stages of food fish. The review process for Indexing is somewhat different than for an approval; an outside panel of experts looks at the drug's safety and effectiveness information. Currently, two products are on the Index (both for aquaculture uses):

OVAPRIM  
AQUACALM

### Extra-Label Use under a Veterinarian

The FDA defines extra-label use as the:

*Actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses.*

Animal Medicinal Drug Use Clarification Act of 1994 allows veterinarians to prescribe approved, but not conditionally approved or Indexed, new animal or human drugs in an extra-label manner when the health of an animal is threatened or suffering or death may result from failure to treat. The law and regulations (21 CFR 530) have specific restrictions on extralabel use, so please contact your veterinarian or consult the regulations for more information.

## Why Read the Label?

It may take a couple of minutes, but it's so important to read a drug's label! The label will tell you exactly how much of the drug to give, how often to give it, how long to give it, and the withdrawal time (how long you have to wait until the fish can be slaughtered, released into public waters, etc.) - all this information is critical to avoid causing illegal residues in the fish that could cause a human food safety concern. In some cases, you may also need to report the use of the drug to your National Permitting Discharge and Elimination Systems authority: the label will tell you when this is the case. The drug's label may also include other precautions that you should be aware of.

## Additional Legal Considerations

Some aquaculture drugs fall under the Department of Homeland Security's (DHS) Chemical Facility Anti-Terrorism Standards (CFATS) and facilities using drugs on the CFATS list must register with DHS.

## Antimicrobial Resistance

Antimicrobial resistance is a growing public health concern. Governments, health professionals, and scientists around the world are working to address this concern.



Some of FDA's efforts to address antimicrobial resistance include evaluation of microbial food safety in the human food safety portion of new animal drug applications, monitoring quantities of antimicrobials sold or distributed for use in food producing animals, and participation in the National Antimicrobial Resistance Monitoring System.

In an effort to promote judicious use of antimicrobials, FDA, working with the American Veterinary Medical Association, published a booklet entitled "Judicious Use of Antimicrobials for Aquatic Veterinarians." The booklet, available online, outlines key principles to consider when using antimicrobials to maximize therapeutic effectiveness and minimize the selection of resistant microorganisms and dissemination of resistance determinants. The guidelines emphasize the importance of:

- Preventative management strategies such as optimal husbandry and use of vaccines
- Veterinary involvement, and
- A proper diagnosis and careful selection of the antimicrobial



## Reporting Adverse Drug Events

If you notice side effects (toxicity, etc.) or find that a drug doesn't work as it's supposed to, it's important to report these "Adverse Drug Events" to the manufacturer. Drug companies, in turn, are required to report adverse drug events to CVM. Using information from these reports, CVM can work with the drug company to modify the drug's label (e.g. to add additional safety precautions) or take other actions as warranted. While FDA carefully considers all the available effectiveness and safety information submitted to the agency before a drug is approved, once the product is on the market and used in a large number of a variety of fish species and culture conditions, previously unobserved adverse events sometimes occur. You play an important role in helping insure the safety of drugs by reporting any problems.



## Where to Find More Information Online

For more information, please visit our website-

Start at FDA's home page at [www.fda.gov](http://www.fda.gov), and select "Animal & Veterinary"

Follow the **Animal Health Literacy Campaign** logo for helpful articles, some geared towards aquaculture and others more general, such as a basic introduction to the drug approval process;

Under **Development & Approval Processes**, you will find helpful links to pages specifically for **aquaculture** and **minor use/minor species**;

Or, follow the **research** link to learn more about aquaculture research at CVM or to access Phish-Pharm, a searchable database of published pharmacokinetic data from fish.

## Contact Information

Questions?  
Email [askcvm@fda.hhs.gov](mailto:askcvm@fda.hhs.gov)

Poster prepared by  
Jennifer Matyszcak, VMD  
May 2011





# What does this mean?



- Only FDA approved drugs can be used for products going to the U.S.
- Drugs can only be used for the species as approved by FDA
  - Sulfamerazine for trout – ok
  - Sulfamerazine for tilapia – not ok
- If drug approved in one country but not by FDA, it is illegal to use for product going to the US



# What does this Mean?



- It is not legal to –
  - Use an antibiotic not approved by FDA for periods of production and then stop using it just before harvest, in hopes the residue is below detectable limits
  - Use a common drug in a manner appropriate for other species and hope the residues do not show up in FDA testing.





# **Animal Drug Approval Process**





# New Animal Drug Application



- New Animal Drug Application (NADA)
- Effectiveness
  - Dose determination, dose confirmation, field studies
- Safety to the target species
  - Toxic syndrome(s), margin of safety
- Human Food safety
  - Short and long term toxicology studies, total residue and metabolism studies, analytical method validation studies, tissue residue depletion studies
- Labeling
- Chemistry, manufacturing and controls
- Environmental Assessment
- Freedom of Information Summary



# Minor vs Major Species



- Major
  - Cattle, horses, swine, chickens, turkeys, dogs, cats
- Minor
  - All other animals, including fish and shellfish



# Guidance for Industry

## FDA Approval of New Animal Drugs for Minor Uses and for Minor Species

**(This version of the guidance replaces the version that was made available on April 15, 1999. This document has been revised to update the contact information, Part 1- Section XI (Other Guides), and minor formatting changes).**

<http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052375.pdf>



# Minor Species Advantages



- Interspecies data extrapolation to help with human food safety studies
- Can use studies submitted to master files
- Conditional Approvals
  - Can make available before completion of effectiveness tests
- Compliance Policy Guide for Extra-Label use of Medicated Feeds for Minor Species
  - Enforcement discretion
- Waivers from User Fees



- FDA may reduce or waive the fees for new minor species applications

ADUFA III FY 2015 Fees	
Animal Drug Application	\$400,600
Supplemental Animal Drug Application requiring safety or effectiveness data and Animal Drug Application subject to criteria in 21 U.S.C. 360b(d)(4))	\$200,300
Product	\$8,075
Establishment	\$104,150
Sponsor	\$94,450



# Extra-label Use



- Use of a drug in an animal in a manner that is not in accordance with the approved labeling.
  - use in species not listed in the labeling
  - use for indications (disease and other conditions) not listed in the labeling
  - use at dosage levels, frequencies, or routes of administration other than those stated in the labeling
  - deviation from labeled withdrawal time based on these different uses.



# Extra-label Use



- FDA allows “extra-label use” under certain conditions
- Must be prescribed by a veterinarian when the health of animal is threatened or suffering or death of animal may result from failure to treat
- Specific restrictions outlined in regulations (21 CFR 530)



# Drugs prohibited for extra-label use

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Dimetridazole, Ipronidazole, and other Nitroimidazoles
- Furazolidone, and Nitrofurazone
- Fluoroquinolones
- Glycopeptides





- It is unlawful to import into the United States animal-derived food that bears or contains residues of a new animal drug that is not approved in the United States, unless:





# Import Tolerance



- ...an **import tolerance** has been established for that new animal drug and the residue does not exceed that tolerance.
- Upon request, FDA can establish a tolerance for residues of new animal drugs not approved for use in the United States, but that are lawfully used in another country





# **Time for a Break!**

Questions?



# **FDA Compliance Programs**



# FDA Approved Aquaculture Drugs

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# Other Prohibited Drugs



- Nitrofurans
- Fluoroquinolones
- Quinolones
- Chloramphenicol
- Malachite green
- Steroid Hormones



FOOD AND DRUG ADMINISTRATION  
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM

7304.018

CHAPTER 04 - PESTICIDES AND CHEMICAL CONTAMINANTS

<b>SUBJECT:</b>  Chemotherapeutics in Seafood Compliance Program *(FY 09/10/11)*	<b>IMPLEMENTATION DATE</b>  10/01/08
	<b>COMPLETION DATE</b>  09/30/11 or until revised
<b>DATA REPORTING</b>	
<b>PRODUCT CODES</b>	<b>PRODUCT/ASSIGNMENT CODES</b>
<u>INDUSTRY CODES:</u> 16 PRODUCT CODES.	<u>REPORT COLLECTIONS AND ANALYSES</u> <u>USING PAC:</u>

FOOD AND DRUG ADMINISTRATION  
COMPLIANCE PROGRAM GUIDANCE MANUAL

PROGRAM

7304.018

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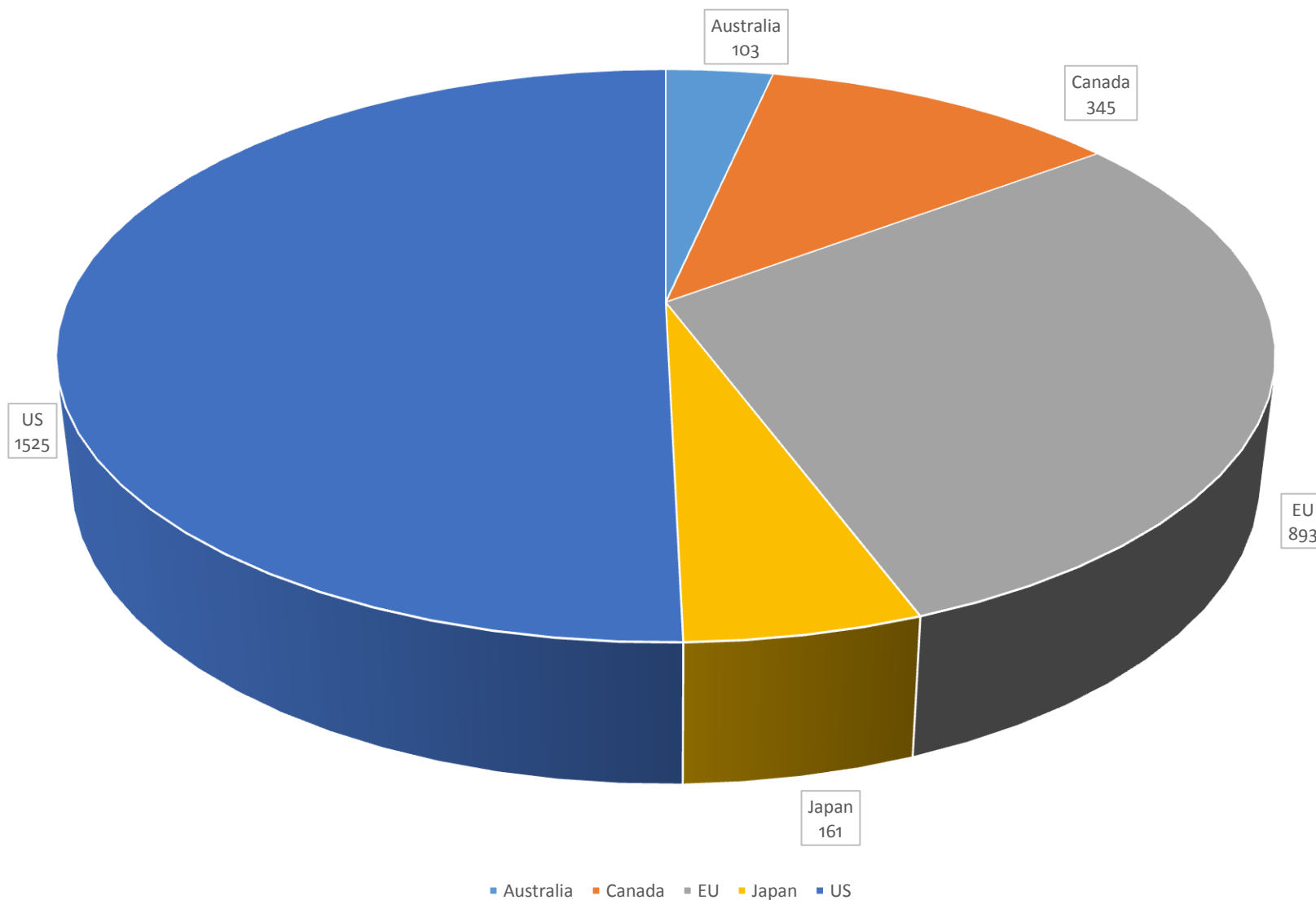




# 2014 Refusals for Residues



3027 Total Refusals, 543 for Drug Residues





# FDA Import Alert 16-124



- "Detention Without Physical Examination Of Aquaculture Seafood Products Due To Unapproved Drugs"
  - Tilapia – malachite green, gentian violet, sulfadiazine
  - Frog legs – ciprofloxacin, enrofloxacin, chloramphenicol
  - Shrimp – chloramphenicol, nitrofurantoin, Fluoroquinolone



# Import Alert 16-127



- "Detention Without Physical Examination of Crabmeat Due to Chloramphenicol"
  - Crustaceans; Crab, Shrimp, Lobster, Crayfish, Langostino



# Import Alert 16-129



- "Detention Without Physical Examination of Seafood Products Due to Nitrofurans"
  - Shrimp and prawns



# Import Alert 16-131



- "Detention Without Physical Examination of Aquacultured Catfish, Basa, Shrimp, Dace, and Eel from China- Presence of New Animal Drugs and/or Unsafe Food Additives"
  - Catfish, Basa, Other Pangasius – Fluoroquinolones, Malachite Green, Gentian Violet
  - Shrimp - Malachite Green, Fluoroquinolones, Nitrofurans, Gentian Violet
  - Dace - Malachite Green, Gentian Violet
  - Eel - Malachite Green, Gentian Violet



# Testing





- LOD- the point at which the analysis is just feasible. Not an Action Level.
- LOQ - Concentration at which the quantitative result can be reported with accuracy and precision.
- Problems with “Chasing Zero”



# FDA's View



- **Q. We know that FDA will take action against a product that contains an unapproved drug when the level is above FDA's LOD (limit of detection). Some private labs have LODs that are tighter than FDA's. What is FDA's view of a test result that show residues that are below FDAs LOD but above the private labs LOD. There is a lot of confusion what this means (is there a residue or not) and what actions a company should take.**
- **A. The Agency bases its actions regarding residues of unapproved drugs in aquaculture products on testing conducted by FDA labs.**
- **Under the Seafood HACCP Plan if a domestic or foreign facility's private lab has discovered an aquaculture residue that contains unapproved fish drug residues the facility would go by the private lab's results that residues have been identified.**
- **The Facility would need to follow their HACCP plan's corrective actions (21 CFR 123.7(a)).**



## **Analysis of sulfonamides, trimethoprim, fluoroquinolones, quinolones, triphenylmethane dyes and methyltestosterone in fish and shrimp using liquid chromatography-mass spectrometry.**

Storey JM, Clark SB, Johnson AS, Andersen WC, Turnipseed SB, Lohne JJ, Burger RJ, Ayres PR, Carr JR, Madson MR

### **Abstract**

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) screening method is described for the detection and identification of 26 veterinary drugs in fish and other aquaculture products. The analytes include: 13 sulfonamides, trimethoprim, 3 fluoroquinolones, 3 quinolones, 3 triphenylmethane dyes, 2 leuco dye metabolites, and 1 hormone. In this method, tissue is mixed with EDTA-McIlvaine buffer, double-extracted with acetonitrile, p-toluenesulfonic (p-TSA) acid and N,N,N',N'-tetramethyl-p-phenylenediamine dihydrochloride (TMPD), and analyzed using LC-MS/MS. Inclusion of p-TSA and TMPD in the extraction procedure was critical for simultaneous analysis of dyes with the other groups of veterinary drugs. The proposed procedure was validated as both a quantitative analysis method and as a semi-quantitative screening method for multiple fish and shrimp matrices. The method was applied to eight types of fish (catfish, eel, pangasius, sablefish, tilapia, swai, salmon, and trout) and shrimp at the appropriate level of concern: 10ng/g for sulfonamides, trimethoprim, and quinolones, 5ng/g for fluoroquinolones, 1ng/g for dyes and their metabolites, and 0.4ng/g for methyltestosterone.



# HACCP Controls

April 2011

## SEAFOOD SAFETY

FDA Needs to  
Improve Oversight of  
Imported Seafood and  
Better Leverage  
Limited Resources



GAO-11-286



# 2011 U.S. Government Accountability Office Study

April 2011

## SEAFOOD SAFETY

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## Why GAO Did This Study

About half of the seafood imported into the U.S. comes from farmed fish (aquaculture). Fish grown in confined aquacultured areas can have bacterial infections, which may require farmers to use drugs like antibiotics. The residues of some drugs can cause cancer and antibiotic resistance. The Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) is charged with ensuring the safety of seafood against residues from unapproved drugs, and the Department of Commerce's National Marine Fisheries Service (NMFS) provides inspection services on request. In 2009, these agencies signed a memorandum of



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**What GAO Recommends**

GAO recommends that FDA study the feasibility of adopting practices used by other entities to better ensure the safety of imported seafood, enhance its import sampling program, and develop a strategic approach for enhancing collaboration with NMFS and better leveraging resources. HHS neither agreed nor disagreed with GAO's recommendations but cited actions in process or planned that are generally responsive to them.



# Seafood HACCP



## CHAPTER 11: Aquaculture Drugs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

*Note: This document was corrected on August 3, 2011. The Agency corrected a typographical error appearing in the April 2011 version of this document. The Agency corrected "15%" to "1.5%" so that the sentence in "Chapter 11: Aquaculture Drugs" now reads "Sodium sulfite Used in a 1.5% solution for 5 to 8 minutes to treat eggs in order to improve their hatchability."*

### UNDERSTAND THE POTENTIAL HAZARD.

Use of unapproved drugs or misuse of approved drugs in aquacultured fish poses a potential human health hazard. These substances may be toxic, allergenic, or carcinogenic, and/or may cause antibiotic resistance in pathogens that affect humans.

general-purpose chemicals, or approved drugs in a manner that deviates from the labeled instructions.

When a drug is approved by CVM, the conditions of the approval are listed on its label or in the labeling (21 CFR 514.1). These conditions specify the species for which the drug is approved for use; indications (disease or other circumstances) for use; dosage regimen; and other limitations, such as route of administration and withdrawal time.



# Suggested Control Strategies



## Primary Processor Controls

- On-farm visit
- Supplier's certification
- Records of drug use
- Drug residue testing
- Quality assurance program

TABLE 11-4

## CONTROL STRATEGY EXAMPLE 4 - DRUG RESIDUE TESTING

This table is an example of a portion of a HACCP plan using "Control Strategy Example 4 - Drug Residue Testing." This example illustrates how a primary processor of farm-raised catfish can control aquaculture drugs. It is provided for illustrative purposes only.

Aquaculture drugs may be only one of several significant hazards for this product. Refer to Tables 3-2 and 3-4 (Chapter 3) for other potential hazards (e.g., environmental chemical contaminants and pesticides).

Example Only  
See Text for Full Recommendations

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
CRITICAL CONTROL POINT	SIGNIFICANT HAZARD(S)	CRITICAL LIMITS FOR EACH PREVENTIVE MEASURE	MONITORING				CORRECTIVE ACTION(S)	RECORDS	VERIFICATION
			WHAT	HOW	FREQUENCY	WHO			
Receiving	Aquaculture drugs	<p>No fish may contain residues of unapproved drugs (other than those used as an INAD subject to an investigational new animal drug exemption under 21 CFR Part 511 and according to requirements of the food use authorization or included on the list of low regulatory priority aquaculture drugs)*</p> <p>No fish may contain a residue level of an approved drug that is above FDA tolerance for that drug*</p>	Fish edible flesh for drug residues*	Obtain samples and analyze for drugs using rapid screening methods or other analytical methods*	Each lot received	Quality assurance personnel	<p>Reject the lot</p> <p>Discontinue use of the supplier until evidence is obtained that drug treatment practices have changed</p>	Analytical results	<p>Periodically verify the adequacy of the testing methods and equipment (e.g., by comparing results with those obtained using an Association of Official Analytical Chemists (AOAC) or equivalent</p> <p>Review monitoring, verification, and corrective action records within 1 week of preparation</p>

\* Note: This plan is for illustrative purposes only. An actual plan should specify: (1) in the Critical Limits column: the aquaculture drugs that are reasonably likely to be present and the critical limits to be applied to each drug; and (2) in the Verification column: the aquaculture drugs for which analysis will be conducted, the protocol for sample collection, and the analytical method to be used for each drug.



# Importer Controls



- Develop and follow written Import Verification Procedures:
  - to ensure product processed in accordance with requirements of 21 CFR 123
  - Develop product specifications for all imported products that are designed to ensure product is not adulterated because it may be injurious to health or processed in unsanitary conditions



- Conduct affirmative steps
  - Regularly inspecting foreign supplier
  - Periodically test product and written guarantee
  - Obtain copies of HACCP and sanitation monitoring records
  - Other appropriate activities
  - Continuing or lot-by-lot certificate from foreign govt or 3<sup>rd</sup> party
  - Copy of HACCP plan along with written guarantee





# Challenges?



# Questions?

Thank you  
[lweddig@nfi.org](mailto:lweddig@nfi.org)