International Regulatory and Trade Issues for Drug Residues in Fish and Seafood

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Introduction

- Increasing demand for fish and seafood
- Wild caught supplies dwindling
- Increasing dependence on aquaculture
- Aquaculture may require the use of agents for control of pests or animal infections
- Misuse of these agents may negatively impact the safety of the product
Introduction

- Internationally, different countries deal with misuse or illegal use of substances differently
- Discuss the issues primarily from US, EU and Canadian approaches
- Try to include implications to regulators, importers and exporters
Warning!!!!

• The following presentation may contain confusing concepts or difficult issues.

• Audience patience and attention is required!
Categories of Agents

- Approved substances
- Unapproved substances
- Banned substances

– Not all jurisdictions have the same interpretation of these terms
Approved Substances

• Agents legally approved for use including provisions for use in aquaculture
  • Use as prescribed does not pose risks
    – Have maximum residue limits (tolerances)
      • May be official MRLs or provisional MRLs
      • Country specific or Codex
    • **May not be the same in every jurisdiction**
      – Importer and exporter responsibilities
Approved Substances?

• Tetracycline (US, Canada, EU)
• Florfenicol (US, Canada, EU)
• Sulfonamides (differs US, Canada, EU)
• Emamectin, Erythromycincin (approved EU with MRL, provisionally approved Canada with aMRL, unapproved US)

– Substances may be approved in one jurisdiction but not another
Approved Substances

• Questions: Are approved agents within the scope of this initiative?

• None, some all?
Unapproved Substances

• Agents not approved for use in aquaculture internationally or within a jurisdiction
  – May be approved in other animals within a jurisdiction but not for aquaculture
    • Ex. Erythromycin, fluoroquinilones
  – May be actually be approved for aquaculture in some jurisdictions not in others
  – May be approved for only certain species within a jurisdiction
Unapproved Substances

– Question: What should be considered unapproved?

– Should unapproved substances be treated as “Zero Tolerance” like banned?
Banned Substances

• Agents that are not approved anywhere for use in food producing animals
  – Agents that are Internationally prohibited nor would ever be considered for use in food producing animals
    • ex. nitrofurans, chloramphenicol
  – Legitimately treated as “Zero Tolerance”
    • No one should be using these!
  – What about MG and CV?
    • Can it be an environmental contaminant?
Banned Substances

– Questions: Which substances should be considered banned?

– Are these residues are to be treated as “Zero Tolerance”?

– Whose definition of “Zero Tolerance”? 
What is “Zero Tolerance”?

• It depends on the country
  – Regulatory Agency method LOQ?
  – No tolerance for any detected/confirmed?

• “Chasing Zero” issues
  – Lab or method shopping

• MRPLs in the EU
  – Minimum required performance limit
MRPLs and Zero Tolerance

• EU has MRPLs (minimum required performance limits) for test methods used to detect these residues
  – Nitrofurans 1 ppb
  – Chlorampenicol 0.3 ppb
  – Malachite green 2 ppb
MRPL Issues

- MRPLs are not MRLs
- MRPLs address the “Chasing Zero” issue
  - Were not intended to be MRLs but may be treated as MRLs
- Action is required for residues below the MRPL….but what action?
  - As a regulator (use is not condoned)?
  - As an importer (do you accept)?
  - As an exporter (why is it there)?
LOQ and “Zero Tolerance”

• Zero as LOQ of the Regulator’s method
  – Zero is defined for the regulator
  – If the regulator is making all compliance decisions…OK

• Residue method performance can vary between labs even with the same method
  – If others are making regulatory decisions….is LOQ OK?
  – “Chasing Zero” or lab/method shopping?
LOQ and “Zero Tolerance”

- EU, when there is no MRL nor MRPL, the LOQ becomes an “Action Level”
- The “Action Level” is to trigger follow up investigations.
- No Action may result from the finding if there are no health concerns with the finding
Risk Based Limits

• At some low concentration, exposure may no longer be considered a risk
• How or who can establish that risk?
  – Codex has considered this for banned substances but within their process they cannot establish an ADI
  – Catch 22…..No amount is acceptable!
Risk Based Limits

• Action limits based on risk have been discussed at QUADs (USA, Canada, New Zealand and Australia discussion group for common interest and possible harmonization, common stand on global issues)
  – Australia and New Zealand (FSANZ) tabled a discussion document for consideration
Risk Based Limits

• Action limits based on risk address health and safety concerns associated with small amounts of residues
• Address the “Chasing Zero” issues
• Still need to decide what you do with product below the limit but with illegal residues
• Example: Health Canada has issued a “No Action” limit for MG/CV of 0.5 ppb based on risk
  – Product can be sold…but do you do nothing?
Legislative Issues

• USA regulations: banned or unapproved residues are a violation and violations legally pose a risk
  – Does not allow for “risk based limits”

• EU and Canadian regulations: banned or unapproved residues are a violation but may not actually pose a health risk
  – A health risk assessment must be done
  – Concept of “technical violations”
  – Allows for “risk based limits”
Generic Method Performance

• Criteria exist in the US and EU for generic elements of a regulatory method that need to be defined when being validated
• Includes MS/MS, MS, UV, etc.
• AOAC criteria, eg. kits, etc.
• These do not specify what the target analytes and concentrations must be
Specific Method Performance

- What are the specific analytes of interest
  - Is it a single residue or a multi-residue method
  - Is it the parent, metabolite, conjugate or total
- What is the target tissue (muscle, kidney, liver, retina, urine, skin, etc.)
- What is the target species (shrimp, tilapia, catfish, salmon, etc.)
- Is there an MRL to guide sensitivity needs
- If not, what is the LOD/LOQ
  - International or specific country requirements
Chloramphenicol

• EU, Canada and US have compliance methods
• All confirmatory methods are HPLC/MS/MS
• All meet the EU MRPL of 0.3 ug/kg
• All target parent compound
Chloramphenicol

• Questions: Is the EU MRPL of 0.3 ppb an agreeable limit?
• Do you want a single residue method for chloramphenicol?
  – Chloramphenicol, thiamphenicol, florfenicol and florfenicol amine multi-residue is possible
Nitrofurans

- EU, Canada and US compliance methods
- Confirmatory methods are HPLC/MS/MS
- Include nitrofurazone, nitrofurantoin, furaltadone and furazolidone
- EU MRPL 1 ug/kg, US LOQ 1 ug/kg
  Canada 0.4 ug/kg minimum required LOQ
Nitrofurans

• Residue markers are metabolites and not the drug residue:
  – nitrofurazone (SEM), nitrofurantoin (AHD), furaltadone (AMOZ) and furazolidone (AOZ)
  – Indirect detection of misuse

• Measurements can be for tissue bound or total residues
  – Tissue bound is indicative of drug use
Nitrofurans

• Tissue bound vs. total residues
  – Important for nitrofurazone metabolite SEM
  – SEM metabolite can have other sources which poses regulatory action problems
    • Eg. azodicarbonamide additive in flour or used in jar lid gaskets
  – Some jurisdictions may not act on positive SEM results
Nitrofurans

• Questions: How low do you want to go?
• Do you want tissue bound or total or both?
• Do you want to include SEM or not?
Fluoroquinilones

• EU, Canada and US compliance methods
• All compliance methods are HPLC/MS/MS
• Common targets include Ciprofloxacin, Enrofloxacin, Sarafloxacin, plus:
  – Difloxacin, Danofloxacin
• Unapproved: US 1ppb LOQ and Canada 0.6 ppb minimum required LOQ
• Approved EU MRL 100 ppb
Fluoroquiniliones

• Question for Panel: How low do you want to go?

• Question for Panel: Which residues do you want as targets?
Quinilones

- EU, Canada and US compliance methods
- Confirmatory methods are HPLC/MS/MS
- Oxolinic acid, flumequine common targets
  - Plus Nalidixic acid in Canada
- Approved: EU MRL (60 ppb FLQ, 10 ppb OXO)
- Unapproved: US LOQ 20 ppb both (10 ppb OXO salmon), Canada 3 ppb minimum required LOQ
Quinilones

• Questions: Which residues do you want to include?
• How low do you want to go?
• Do you want to explore a multi-residue method for both quinilones and fluoroquinilones?
Malachite Green and Crystal Violet

- EU, Canada and US compliance methods
- Confirmatory methods are HPLC/MS/MS
- Targets are MG, CV and the reduced LMG and LCV forms
- EU MRPL 2 ppb, US 1 ppb LOQ
  - Zero tolerance
- Canada 0.5 ppb minimum required LOQ
  - Not a zero tolerance
Malachite Green and Crystal Violet

• Canada has a “No Action” limit for residues below 0.5 ppb
  – Health Canada interim limit 1.0 ppb
    • No health risk below 1 ppb
    • Based on the assumption that there may be other non-drug use sources, possibly environmental
Malachite Green and Crystal Violet

- Canada has a “No Action” limit for residues below 0.5 ppb
  - Health Canada interim limit 1.0 ppb
    - No health risk below 1 ppb
- MG and CV are quickly reduced in vivo to Leuco forms which predominate findings
  - MG and CV alone may signify post-harvest treatment or contamination of samples
Malachite Green and Crystal Violet

- Questions for Panel: Do you need a method for MG/LMG and CV/LMG?
- How low do you need to go?
- Do you want to include other Triphenylmethane dyes, eg. Brilliant Green?
Methyltestosterone

- Not allowed for use in EU, Canada nor US
  - Likely will not be approved for aquaculture anywhere in the world
- US FDA does test for this residue
- Canada does not have a method
- EU likely has methodology for steroids in fish
Methyltestosterone

- Question for Panel: Do you need a method for methyltestosterone?
- Do you want to look for other similar compounds?
- How sensitive should this method be?
Other Drugs?

- Tetracyclines?
  - EU MRLs for tetracycline, chlortetracycline and oxytetracycline
  - US looks for oxytetracycline (sum of all three) in shrimp
  - Canada MRL for oxytetracycline (approved) in salmon and lobster, also look for chlortetracycline and tetracycline (unapproved)
Other Drugs?

• Avermectins?
  – EU MRL 100 ppb for emamectin in salmon, ivermectin is unapproved
  – US looks for ivermectin
  – Canada aMRL 42 ppb for emamectin in salmon, also look for ivermectin (unapproved)
    • require 2 ppb minimum LOQ for both
Other Drugs?

- Sulfonamides?
  - EU MRL 100 ppb total for sulfonamide group
  - US Sulfadimethoxine/ormetoprim and Sulfametazine are approved
  - Canada MRL 100 ppb for Sulfadimethoxine, Ormetoprim, Sulfadiazine, Trimethoprim in salmon but look for another 15 unapproved
Technologies

- Confirmatory methods discussed have all been HPLC/MS/MS
- Regulatory methods may be non-MS type
  - Eg. US FDA has a quantitative MG/CV method based on LC/UV
    - Violative results must be confirmed by MS
    - May be suitable for industry QA
  - Screening methods like ELISA immunoassay
    - Need confirmations but offers affordable and flexible tools to industry or in the field
Reference Methods

• Regulators have their own national compliance and confirmatory methods
  – Not all the same

• Questions: Do you want an AOAC validated reference method for any or all of the drugs of interest?
• If so, how can that be achieved?
Screening Methods

• Responsibility for the safety of food is not just for Regulatory Agencies
  – Industry has an important role
  – Industry must be a partner for food safety

• Question: Do you want screening tools developed for industry to use at key or critical points in the supply chain?
Example CFIA Contract
Performance Specifications

- An accredited analytical method equivalent to CFIA reference method 064-2 Tetracyclines in Tissue by HPLC
- Sample is extracted with buffer, filtered, passed through an SPE column, rinsed with water prior to elution with methanolic oxalic acid.
- Instrumental analysis is by HPLC/PDA
Example CFIA Contract
Performance Specifications

• A detection limit of 0.025 ppm or less for tetracycline and oxytetracycline and 0.05 ppm or less for chlortetracycline is required in the following food groups:
  – Dairy, egg and meat (muscle tissue)
  – Methods not providing this DL for the three analytes in all food groups will be rejected
Example CFIA Contract Performance Specifications

• Confirmation using an acceptable MS technique is required for all samples found in violation of the Canadian maximum residue limits for the specific drug/commodity combination by the initial method
Example CFIA Contract Performance Specifications


Example CFIA Contract
Performance Specifications

• Variations of contract specs must include relevant criteria specific to the testing requirement:
  – Nitrofurans: must include hydrolysis and derivitization steps to release protein bound metabolites (AOZ, AMOZ, AHD and SEM)…
  – Others may list specific tissues: eligible food groups include tissue (muscle, liver and kidney)
Closing Comments

• Zero tolerance is a big problem to manage
• Regulators need to have the risks for residues at low levels defined
  – At some level, even banned substances likely do not pose a risk
• Producers and importers need to know the requirements of their own country
• Importers need to know their suppliers and specify to them what is needed
Closing Comments

- Exporters and Importers need to know what are the requirements of the country they are doing business with.
- Need better inspection systems and production controls in some overseas countries.
Who Needs What?

• Regulators have compliance methods for many of the residues of concern
  – Do they need an AOAC validated Reference Method?

• Industry needs tools to for their own use
  – Does industry want an AOAC validated Reference Method?
  – Does industry want rapid screening methods?