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Addressing Antibiotic Resistance From Farm-Raised Fish Imported To The United States

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Addressing Antibiotic Resistance From Farm-Raised Fish Imported To The United States

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Abstract

Misuse of medically important antibiotics in animal production threatens the effectiveness of drugs that are vital in combating disease and infections. Recently, the FDA implemented regulations to limit the use of and access to veterinary drugs. However, these regulations only affect domestic production operations. Because over 90% of seafood consumed in the U.S. is imported from countries with different regulatory standards and because the U.S. has an import inspection rate of less than 1%, antibiotic resistance stemming from imported aquaculture is still a risk that is not sufficiently accounted for. This research investigates how the U.S. has reacted to the growing issue of antibiotic resistance and explores how to further reduce bacterial resistance contributed by aquaculture imports. In addition, it demonstrates that imported fish from aquaculture production presents a risk to human health, undermining progress in U.S. regulatory control of antibiotic use. Actions taken by the FDA in recent years to curb antibiotic use is presented to illustrate the United States' overall response and current strategy. Then a review of scientific research identifying evidence of antibiotic use and import rejection data from the FDA was used to assess the threat of resistance from imported aquaculture. The research verifies that medically important drugs are being used in aquaculture by the countries from which the U.S. imports most of its seafood. Drawing recommendations based on current E.U. policy, to better account for antibiotic resistance from imported aquaculture, the U.S. should involve exporting country authorities in trade operations to increase the degree to which U.S.-bound seafood is inspected. Greater funding to increase inspection upon arrival in the U.S. should also be allocated. Additionally, research on antibiotic alternatives should also be heavily supported as well advocacy for veterinary-style legislation in countries that do not already moderate the use of and access to antibiotics for aquaculture. Bacterial resistance from imported aquaculture is still an issue is of concern that is adequately addressed under U.S. regulations.

Executive Summary

In 2015, imports accounted for approximately 90% of all seafood consumed in the U.S., with over 50% of all seafood imports produced through aquaculture (National Oceanic and Atmospheric Administration, 2016). Total aquaculture production is expected to surpass catch fishery production in 2021 (The Organization for Economic Cooperation and Development, 2016). The majority of aquaculture producers in globally use antibiotics to mitigate the risk their fish face while being grown in confined animal feeding operation (CAFO) settings. The frivolous use of antibiotics in animal husbandry is largely to blame for the emergence of resistant bacteria and infection incidences. If fish imports from weakly regulated countries continue, the health benefits of new antibiotic regulations in the U.S. may be undermined. This thesis assesses the efficacy of our national policy in curbing the spread of bacterial resistance, particularly from imported aquaculture. Policy recommendations are also put forth on ways the U.S. can take steps to further address bacterial resistance in this food source.

Aquaculture is a fish-farming practice that uses controlled breeding along with nutrient and medical supplementation to support fish development (Sapkota et al., 2008). In aquaculture, animals are mostly grown confined in enclosures with a high abundance of other fish. Animals in these operations often feed and defecate in the same location, exposing the fish to bacteria in fecal matter. Because of conditions like these, animals in the operation are more susceptible to bacterial, fungal, and viral infections (Rigos et al., 2005). Antibiotic application during fish development is the most commonly used technique in aquaculture to combat bacterial growth and mitigate the spread of infection (Sapkota et al., 2008).

According to NOAA, shrimp, tuna, salmon, and tilapia are the most eaten seafood in America, all of which are primarily imported (NOAA, 2015). In the U.S., low rates of inspection of seafood imports render consumers vulnerable to contaminated or tainted goods. In 2014, fish was found to be the most frequent origin of foodborne illness outbreaks (Centers for Disease Control, 2016). The United States Food and Drug Administration (FDA) is responsible for ensuring the nation's food safety through supervision of most food products and pharmaceuticals, while the United States Department of Agriculture (USDA) is responsible for protecting the nation's egg, meat, poultry, and produce supply (Koonse, 2016; USDA, 2016). Because the majority of seafood consumed in the U.S. originates from foreign production, the FDA performs foreign country assessments on countries involved with aquaculture trade to the U.S. The FDA has set safety standards and protocols that registered foreign producers are required to abide by to ensure eligibility for trade. However, FDA does not inspect foreign production facilities regularly, and instead foreign inspection is primarily done by third-party agencies that are certified by the FDA. Continued foreign antibiotic use in imported aquaculture imposes a threat of bacterial resistance that current U.S. inspection practices do not account for.

Bacterial resistance is a natural biological occurrence that is being exacerbated by exposure to antibiotics. When bacteria or other microorganisms are frequently exposed to low doses of antibiotic drugs, they either die or grow immune to the effects of that drug (FDA, 2015h). As bacteria become resistant to antibiotics, standard treatments lose effectiveness (World Health Organization, 2016). Bacterial resistance from antibiotic overuse has been an issue of concern, especially since some antibiotics used in confined animal operations are also prescribed for human use. Since common antibiotics that are used to fight

human infections are often used in aquaculture, bacterial resistance from antibiotic overuse could potentially compromise the effectiveness of many antibiotics important in modern medicine (Heuer et al., 2009). There are two pathways for resistance to spread. First, resistant bacteria can enter the food chain when humans consume contaminated animals. Second, drugs that enter the food chain can allow bacteria to develop resistance once in humans or in the environment. Chemical and drug residues are transferred from treated, farmed-fish to consumers and the environment where resistance can develop among new bacteria (FDA, 2015a). This has contributed to the general decline in effectiveness of antibiotics and the increase in "super bugs" or multi-drug resistant bacteria.

Over time, the FDA has taken some limited steps to address bacterial antibiotic resistance. In 2015, the FDA legally mandated its recommendations introduced in previous guidance directives by introducing legislation to restrict the use of antibiotics for medicinal uses, such as disease and infection defense, making it illegal to use drugs for production enhancement. The Veterinary Feed Directive (VFD) final rule is the most recent action by the FDA to curb the spread and rapid progression of bacterial resistance and came into effect in January of 2017. The goal of the rule is to reduce inappropriate overuse of antibiotic drugs in animal production (Veterinary Feed Directive, 2015). The VFD was a significant step towards slowing resistance, especially due to the large amount used in the U.S. not only in aquaculture but in livestock production as well. Although the FDA has been active in addressing antibiotic use domestically, a significant portion of all seafood consumed in the U.S. is imported. Because there are far fewer production regulations in the countries that import seafood to the U.S., it is highly likely that antibiotics are in frequent use in many foreign aquaculture operations. As a result, because so much seafood is imported with

potentially resistant bacteria, efforts by the FDA to control antibiotic resistance will ultimately be undermined.

Three cases of imports of farm-raised fish were investigated to assess evidence of contamination of imported fish product: shrimp, salmon, and tilapia. India and Indonesia are the top shrimp-producing exporters to the U.S., accounting for 25.4% and 19.4% of all shrimp imported in 2016. Recent instances of discovered antibiotic use indicate gaps in governance over shrimp farming in both India and Indonesia, posing health risks to U.S. consumers. In 2016, the U.S. rejected 114 lines[1] of shrimp from Indian exporters for a variety of violations, including drug residues. Of those rejected lines, 95 were rejected for the presence of an illegal veterinary drug. In 2015, the U.S. instituted import alerts for specific Indonesian producers as multiple shipments exhibited residues of nitrofurans and enrofloxacin, two medically important antibiotics (FDA, IRD, 2017). From both of these countries, recent instances of discovered antibiotic use indicate that there are undoubtedly some gaps in governance over shrimp farming in both India and Indonesia posing health risks to U.S. consumers.

Salmon is the third most popular seafood type in the U.S., and Chile and Canada are major producers of Atlantic salmon, accounting for large portions of U.S. salmon imports. Although there have been multiple rejections from Canada and Chile for salmon in 2016, there were no rejections on the basis of antibiotic evidence. However, evidence of antibiotic use through the presence of multiple resistant bacteria was identified in Chile (Buschmann et al., 2012). Aquaculture regulation in Chile and Canada differ substantially. Chile has weak regulation enforcement and has no direct regulatory mandates in place to specifically address

[1] Each line refers to a shipping container, containing between 36,000 – 40,000 pounds (Hindu Business Line, 2015).

antibiotic usage. Conversely, Canada has a veterinary drug system identical to the one the U.S. has recently adopted.

China was the source of 73.6% of all U.S. tilapia imports in 2016. In addition to producing the most aquaculture globally, China accounts for 36% of all tilapia produced (FAO 2015). Chinese sourced tilapia purchased in the U.S. was found to have oxytetracycline residues, but at concentrations of less than 1 ppm, under the legal limits permitted by the FDA (Done & Halden, 2015). Although oxytetracycline is banned in China, residues isolated residues from samples of farmed tilapia indicate illegal drug use even with government regulation in place.

Reviewing this import rejection data, it is evident that exposure to antibiotic residues and resistant bacteria are risks presented to American consumers as a result of insufficiently regulated aquaculture imports. Despite cases of identified resistant bacteria in all production regions, rejection evidence for antibiotic use in shrimp is most prevalent, whereas evidence for antibiotic use for salmon and tilapia is comparatively weaker. Policies are needed to address bacterial resistance from imported seafood. Increasing physical inspection rates of imports is an early step the FDA can take to reduce the U.S.'s susceptibility to antibiotic resistance from imported aquaculture. Because of their inspection rates, I referred to the E.U. for insight on ways to enhance current U.S. inspection and import procedures.

Compared to the U.S., the E.U. inspects at least 20% of its imported seafood (Love et al., 2011; Vrignaud, NOAA, 2013). Aquaculture importing procedures differ between the U.S. and the E.U. with the E.U. allowing for greater inspection and auditing opportunities of foreign producers. E.U. import authorities only accept imports from specific exporters that have been recognized by its government authority and have thus been authorized by E.U. All

government agencies that operate under the guidelines of the E.U. must show they have adequate jurisdiction, resources and ability to perform thorough inspections of all stages of the supply chain in their country. In comparison, the FDA does not require the involvement of the exporter's government authority.

Drawing on policy options from the E.U to address risks of antibiotic resistance associated with imported farmed fish, the FDA should develop stronger relationships with "competent authorities" of U.S. trade partners and involve them as enforcers of food safety regulation in the trade process. In addition, the FDA should increase inspection rates upon product arrival. Increasing import inspection rates is the simplest domestic change the U.S. can enact on its own. Furthermore, international organizations and government authorities should advocate for veterinary-style legislation in all exporting countries. Because bacterial resistance is a global issue, a unified, international push to restrict access to and use of antibiotics can be vital in changing current antibiotic use practices. Finally, more research should be focused toward alternatives to antibiotic use in aquaculture. Effective alternatives to antibiotics can help producers' transition away from medically important drugs.

Chapter I: Introduction

A heightened demand for fish due to growing populations, enhanced trade systems, and urbanization have supported the expansion of fish farming (Food & Agriculture Organization, 2014). As a comparatively more efficient way of obtaining fish than catch methods, aquaculture is increasingly used to meet demand and currently accounts for nearly half of all fish food consumed internationally (FAO, 2014). Aquaculture is a fish-farming practice that uses controlled breeding along with nutrient and medical supplementation to support fish development (Sapkota et al., 2008). Over 600 different species of aquatic animals are developed through aquaculture (Troell et al., 2014). These include finfish, crustaceans, mollusks and aquatic photosynthetic organisms. The global aquaculture output has doubled between 2000 and 2013 from 34.4 million tons annually to 70.2 million tons, compared to 92.6 million tons of wild caught fish, in 2013 (FAO, 2014). Total aquaculture production is expected to surpass catch fishery production in 2021 (The Organization for Economic Cooperation and Development, 2016).

In most aquaculture operations the risk of bacterial infections is higher than that of wild caught fish due to high fish densities and ineffective separation between farms (Naylor & Burke, 2005). In aquaculture, animals are mostly grown confined in enclosures with a high abundance of other fish. Animals in these operations often feed and defecate in the same location, exposing each to bacteria in fecal matter. Because of conditions like these, animals in the operation are more susceptible to bacterial, fungal, and viral infections (Rigos et al., 2005). Antibiotic application during fish development is one commonly used technique in aquaculture to combat bacterial growth and mitigate the spread of infection (Sapkota et al.,

2008). Producers who use confined feeding spaces are inclined to do this rather than risk the chance of seeing their stock deplete due to disease or infection. In tandem with a growing aquaculture industry, in the last thirty years there has been a recognizable increase the amount of multi-drug resistant bacteria strains discovered in seafood (Done & Halden, 2015). Bacterial resistance from antibiotic overuse has been an issue of concern, especially since some antibiotics used in confined animal feeding operations are also prescribed for human use. Since common antibiotics that are used to fight human infections are often used in aquaculture, bacterial resistance from antibiotic overuse could potentially compromise the effectiveness of many antibiotics important in modern medicine (Heuer et al., 2009).

In 2015, imports accounted for approximately 90% of all seafood consumed in the U.S., with over 50% of all seafood imports produced through aquaculture (National Oceanic and Atmospheric Administration, 2016). The most imported types of seafood, by volume to the U.S., were sourced primarily from Asian countries in the Pacific Rim. While this helps to satisfy the increasing demand for fish in the U.S., each country maintains differing and comparatively less stringent drug use restrictions in aquaculture compared to the U.S. (NOAA, 2016). There is concern that due to weak health and environmental standards regulating aquaculture in foreign countries, imports may represent a significant health threat, particularly with respect to antibiotic residues. Due to the urgent nature of growing antibiotic resistance, animal production operations in the U.S. are now being more tightly regulated. Beginning in 2017, U.S. animal operations, including aquaculture, will be restricted in the amount and types of antibiotics allowable. If fish imports from weakly regulated countries continue, the health benefits of new antibiotic regulations in the US may be undermined.

Understanding the severity of the bacterial resistance from antibiotic overuse, the Food and Drug Administration (FDA) has recently been active in setting new regulations to limit the abundant use of antibiotics in U.S. confined animal feeding operations (CAFO). In most operations, healthy animals had been administered antibiotics regularly in low doses not only to defend against infectious bacteria but also to promote growth (Defoirdt et al., 2011). It is important to note the classification distinction between medically important drugs and drugs used in animal production. Medically important drugs are drugs that are used to fight diseases and infection in humans (FDA, 2015a). Many of these same drugs are also used in CAFOs as prophylactics (Defoirdt et al., 2011). Bacteria that survive extended, low concentration antibiotic exposure can grow resistant to the drug. There are two pathways for resistance to spread. First, resistant bacteria can enter the food chain when humans consume contaminated animals. Second, chemical and drug residues are transferred from treated, farmed animals to consumers and the environment where resistance can develop among new bacteria (FDA, 2015a). This has contributed to the general decline in effectiveness of antibiotics and the increase in "super bugs" or multi-drug resistant bacteria. By restricting the use of any medically important antibiotics that enhances animal production, and by monitoring the use of all antibiotics used only for treatment, the FDA intends to curb the progression of antibiotic resistant bacteria (FDA, 2015b).

However, antibiotics that are banned in the U.S. may be permitted for aquaculture in partnering trade countries. Currently, a significant portion of seafood that enters the U.S. is sourced from countries with weak or nonexistent regulations to slow antibiotic resistance. Therefore current trade trends aid the progression and dispersal of resistant bacteria in the U.S., which have adverse impacts on the health of Americans.

This thesis assesses the efficacy of U.S. national policy in curbing the spread of bacterial resistance, particularly from imported aquaculture. Specific focus is placed on seafood imports, over half of which were produced through aquaculture. Further emphasis is placed on shrimp, salmon, and tilapia, as they are the most consumed U.S. seafood imports (NOAA, 2016). Reports of antibiotic use and residue identification obtained from imported seafood are used to help illustrate the degree to which current trade may undermine the effectiveness of U.S. regulations on health and safety.

The following chapter discusses current U.S. consumption and trade trends with respect to seafood, followed by a review of the regulations in place to inspect imported goods. Afterward, the topic of bacterial resistance as a result of antibiotic overuse and the actions taken by the FDA to address it are discussed. Three case studies are then analyzed based on reports of antibiotics used in specific seafood trading countries to determine if current U.S. policies are sufficient to curb bacterial resistance that may stem from imported aquaculture. Reports of drugs used and evidence of drug residues in shrimp from India and Indonesia, salmon from Chile and Canada, and tilapia from China provide insight on the human health risks associated with the amount and different types of antibiotics used in imported aquaculture. Lastly, policy recommendations are put forth on ways the U.S. can take steps to further address bacterial resistance in this food source.

Chapter II: U.S. Seafood Import Regulations and Inspection Procedures

2.1 U.S. Seafood Import Trends, Procedures & Regulatory Framework

Today, the vast majority of seafood consumed in the U.S. is imported. In 2015, imports accounted for about 90 percent of all seafood consumed in the U.S. (National Oceanic and Atmospheric Administration, 2016). Most seafood imports to the U.S. originate from Asia and about half of all imported seafood is produced from aquaculture. Seafood production from aquaculture has increased more than 45 percent since 1970 and currently accounts for 50 percent of all seafood consumed globally (NOAA, 2016; Sapkota et al., 2008). Every year seafood consumption and therefore imports continue to increase in the U.S. (NOAA, 2016).

According to NOAA, shrimp, tuna, salmon, tilapia are the most eaten seafoods in America, all of which are primarily imported (NOAA, 2015). In 2016, India, Indonesia and Thailand were the three countries from which the U.S. imported the most shrimp, followed by Vietnam then China. These countries accounted for 72 percent of all shrimp imports to the U.S. last year. China alone produced 73 percent of all imported tilapia (NOAA, 2016).

Low rates of inspection of seafood imports render consumers vulnerable to contaminated or tainted goods. In 2014, fish was found to be the most frequent origin of foodborne illness outbreaks (Centers for Disease Control, 2016). Without action, internationally sourced resistant bacteria will spread, especially since imports are projected to continually increase in coming years (NOAA, 2015). In order to address this concern, the U.S. has worked to enhance existing regulations to manage imports and perform inspections to evaluate the safety of foreign-sourced goods.

In the United States, the Food and Drug Administration (FDA) is responsible for ensuring the nation's food safety through supervision of most food products and pharmaceuticals, while the United States Department of Agriculture (USDA) is responsible for protecting the nation’s egg, meat, poultry, and produce supply (Koonse, 2016; USDA, 2016). Accordingly, each agency is responsible for the labeling and inspection of their respective goods, though they often work in collaboration on several mutually benefiting initiatives. Prior to 2002, all imports were received by the Center for Border Patrol without any advanced notification. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 mandated FDA to require prior notice before accepting shipments for inspection (FDA, 2009). Before this Act, shipments would arrive at U.S. ports and information from the sender and of the shipment would be assessed at that point. This prior notice required the importer's contact information be presented in advance along with product information, much of which was not known until the date of inspection before the act. Prior notice benefits the FDA first by allowing inspectors more time to review and examine the sender's history and product information before its arrival, and second, by allowing the agency to better manage its resources for inspections (FDA, 2009). Currently, all importers must be registered with the FDA and provide an advance notice of the imports in order to receive the opportunity to have their goods reviewed for inspection.

In 2011, the HACCP inspection procedure was enhanced under the Food Safety Modernization Act (FSMA). The Act placed emphasis on inspection, compliance, preventive controls, response, import safety, and enhanced partnership (FDA, 2015d). The new legislation required that importers engage in preventative practices based on the estimated risk associated with their product in efforts to ensure the safety of their imports. To enforce

hazard accountability on producers, the Act required the FDA to develop a tracking system to record the location and the processers that the seafood originated from. Additionally, the FMSA required the FDA to expand its capacity by consulting with consumers, producers, stakeholders and federal officials from exporting countries to further enhance food safety and regulation (Koonse, 2016). FDA has developed relationships with partner organizations to certify that foreign production facilities are in compliance with U.S. regulations (FDA, 2015d).

2.2 Inspections at the foreign source

Since the majority of seafood consumed in the U.S. originates from foreign production, the FDA performs foreign country assessments on countries involved with aquaculture trade to the U.S. The benefit of these assessments is that they provide insight on the level of competency and regulatory power of the assessed country as well as the country's aquaculture trends (FDA, 2015c). Foreign assessments are vital to determining risk for particular imports and for identifying drug use in aquaculture operations. Risk and drug use information obtained during these assessments allow the FDA to prioritize their resources more effectively (FDA, 2015c). It also allows the FDA to collaborate with foreign agencies to attempt to rectify the drug use violation. Based on assessment the FDA gains insight on whether to alter current international surveillance tactics or to alter its sampling and analysis procedures to target different drug types.

The FDA maintains safety standards and protocols that registered foreign producers are required to abide by to ensure eligibility for trade. Currently, domestic and international seafood producers who sell within the U.S. are required to have a Hazard Analysis and

Critical Control Point plan (HACCP) (FDA, 2015c). As the primary standard that serves as the foundation for the FDA's inspection process, the plan is intended for processors to detail the specific parts of their production process that could potentially expose the seafood product to contamination. The producers must also develop new protocol to address the hazard and demonstrate that they have been in compliance. The FDA performs evaluations of fish farm operations using the facilities HACCP plan as the primary basis for judgment (Koonse, 2016). These evaluations are done electronically when the prior notice itinerary is received by the FDA. By forcing producers to highlight their most unsafe part of production, FDA inspections can evaluate if the farming operation accurately recognizes vulnerable stages of their production process and if they have taken the steps to effectively address it.

FDA does not inspect foreign production facilities regularly. Between the years 2005 – 2010, FDA inspected 503 international aquaculture production and processing facilities out of an estimated 17,000 that had exported seafood products with the U.S. over that time (GOA, 2011). Foreign inspections are generally contingent on the specific country's violation history, export volume, importer compliance, producer credibility and technological uses (FDA, 2015e). International surveillance by the FDA consists of physical product examination, chemical analysis of sample collections, and reviews of past inspections for importing countries (FDA, 2015e).

FDA prioritizes its resources based on risk analyses of seafood products. Production, packaging, storage, and intended state of consumption are all considered when determining the risk of a product (FDA, 2015e). The actions of import are observed and also influence resource prioritization. Importers that continually import from foreign facilities that have a faulty safety record would be inspected more frequently than the average processing plant

(Koonse, 2016). Subsequently, the risks associated with specific products are largely influenced by the countries' overall recorded history of seafood safety infractions.

In addition to maintaining the authority to request certain foods be inspected at certified laboratories, FDA also coordinates with third party agencies to perform physical inspections at international facilities (FDA, 2015d).

FDA first certifies third-party agencies that assist in inspection, before verifying them with U.S. importers. Third-party certification is not required by the FDA for entry in the U.S. However, in certain cases the FDA requires a certification from a third-party organization before allowing the import into the country. This is usually contingent on the violation history of the exporting country. Similar to international fish farm facilities, the FDA performs inspections and evaluations on domestic import companies and their facilities as well. U.S. based importers must bear some responsibility to ensure consumer safety as well. U.S. importers are mandated to possess the HACCP of every foreign facility that they receive seafood from (FDA, 2015c). Though not required, some importers also inspect the facilities that they work with to ensure the facility is in compliance with U.S. safety measures. Additionally, other importers rely on safety certification from external inspection agencies accredited by the FDA or by foreign governments (Koonse, 2016). Although certification is not mandatory, it does make the production source more appealing to U.S. based importers and is generally entered into the U.S., with ease and limited further inspection.

2.3 Procedures upon arrival in the US

Before shipments that are under FDA regulation reach the U.S. shores, prior notice of the import must be given to the FDA. This is done electronically, which allows importer

information to be traced. Each shipment is electronically screened using a risk-based analysis system. FDA uses a Predictive Risk-Based Evaluation for Dynamic Import Compliance Targeting (PREDICT) system to analyze recorded import data for foreign facilities and assess their product risk potential (GOA, 2016). Once prior notice of a shipment is received, the FDA can cross-check the import data received which generally includes previous sample analysis results, facility inspection history, and product type. The PREDICT software aims to pinpoint data inconsistencies that allow FDA to place a particular facility on high alert for inspection (Koonse, 2016). Electronic analyses of import entries are scanned for incomplete or questionable information, as well as evaluated on the import's overall risk potential. Seafood sourced from violation-free exporters or from low-risk product often enters the country unchecked.

All incoming shipments are received by the U.S Customs and Border Protection (CBP). Tariffs are collected and FDA prior notice documentation is required before the goods are accepted (FDA, 2015b; CBP, 2016). All accepted goods are then transferred from the CBP to import services in the U.S. for distribution. Generally, external arrangements are already made for domestic importers to physically receive the goods. The PREDICT system guides FDA physical inspection. The FDA only intercepts shipments that the software has calculated to be a potential threat. The FDA alerts the CBP and authorities receive shipments which are then sent to one of FDA's 13 laboratories for analysis (GOA, 2011). All shipments are screened, but few shipments are inspected.

Once FDA obtains shipments, seafood undergoes a microbiological examination and chemical analysis. Microbiological examinations test for pathogens, where a chemical analysis examines the presence of additives, product decomposition, drugs, metals, or

pesticides (FDA, 2015g). There are several different examination procedures for 22 different bacterial strains in the Bacteriological Analytical Manual, or BAM (FDA, 2015g). The FDA also has standard individual examinations for drug residues, testing for a short list of 10 identified drug and chemical residues in seafood. Because examinations target specific residue types, the agency is able to determine the individual antibiotics in a sample. Residue analyses require several different solvents and additives, as well as extraction techniques. Commonly used analytical techniques include chromatography and spectrometry (FDA, 2015g).

Finally, the FDA holds the authority to place processors that have been found to violate U.S. safety standards on an Import Alert (FDA 2015e). FDA developed a public alert platform to notify consumers, private importers, and FDA import inspectors of potentially tainted goods. In the alert, products from specific producers that have shown repeated instances of contaminated or tainted shipments are reported in the alert and all products received from those producers are to be immediately removed from the market and shipments be confiscated at the border. For a producer to be removed off of an import alert they must identify and rectify the processing facility hazard and demonstrate it to the FDA (Koonse, 2016).

Fortunately, the FDA has recognized the health detriments connected with antibiotic overuse and have taken more recent steps to address the worsening issue. However, although FDA has a process in place for inspecting fish imports and for evaluating foreign producers, there is evidence indicating that it is not stringent enough. Given the recent significant improvements in U.S. controls on the use and access of antibiotics in animal agriculture, as

detailed in the following chapter, there is a need to harmonize the requirements of imports with the standards now enforced within the U.S.

Chapter III: Bacterial Resistance and the FDA's Efforts to Combat it

3.1 Concern over Bacterial Resistance

Bacterial resistance is a natural biological occurrence that is being exacerbated by exposure to antibiotics. When bacteria are frequently exposed to low doses of antibiotic drugs, they either die or grow immune to the effects of that drug (FDA, 2015h). As bacteria become resistant to antibiotics, standard treatments lose effectiveness (World Health Organization, 2016). Overuse of antibiotics will lead to longer lasting and more complex infections, resulting in deadlier consequences (FDA, 2016b). Already, bacteria linked to meningitis, pneumonia, specific skin infections and urinary tract infections have shown evidence of drug resistance (FDA, 2016b; Tavernise, 2014). Annually, two million people are infected with antibiotic-resistant bacteria and on average 23,000 people die as a direct result of these infections, in the United States alone. Existing medical issues combined with infections from resistant bacteria possibly contribute to even more deaths per year (Center for Disease Control, 2013).

The frivolous use of antibiotics in animal husbandry is largely to blame for the emergence of resistant bacteria and infection incidences. Arguably, over-prescribing of antibiotics for human use also contributes to the bacterial resistance. According to the former FDA commissioner, David Kessler, in 2011 of the thirty million pounds of antibiotics that were purchased in the U.S., about twenty-four million pounds of antibiotics were used for animal production, which is roughly 80% (NYT, 2013). This is concerning as domestic animal antibiotic sales and distribution have increased by 26% from 2009 – 2015 (FDA, 2016e). Animal antibiotics have long been used for livestock production and for decades

have been labeled by drug manufacturers as a growth stimulator as well as a medicinal agent to combat bacterial infection. Because of this, producers have had the authority and incentive to regularly use antibiotics to accelerate the growth of their animals as well as to prevent infections or disease (FDA, 2015h). Antibiotics are typically administered as a blend with animal feed or as a solvent in water to all healthy animals. Because antibiotic application in this manner for growth promotion has been standard practice in CAFOs, the amounts used have grown to an enormous quantity creating high selective pressure on resistant bacteria.

There are two pathways of bacterial contamination transfer from animal to human. Bacteria can develop resistance in the animal and then persist in the food product, or the antibiotic drug itself may survive the intestine of the animal and persist in the animal tissue, in which case the consumer is ingesting traces of the antibiotic potentially leading to bacterial resistance within themselves (Santos & Ramos, 2016). Through either avenue of exposure, once in the body bacterial resistance has the capability to rapidly spread between bacteria through a biological mechanism called “conjugation”. Certain resistant bacteria can pass along their resistance gene, as well as other genes to other proximate bacteria, increasing the overall abundance of resistant bacteria within humans, animals and the environment (CDC, 2013). Furthermore, exposure can occur due to manure from drug-treated animals polluting waterways. This is a common way in which bacteria spreads and how outbreaks occur in communities. Generally, for humans, bacterial outbreaks result from ingested pathogens present on unsanitary foods (CDC, 2013).

3.2 Early Efforts to Regulate Antibiotic use in Animal Agriculture

Over time, the FDA has taken some limited steps to address bacterial antibiotic resistance. In 1996, in conjunction with the Center for Disease Control (CDC) and the U.S. Department of

Agriculture (USDA), the FDA created the National Antibiotic Resistance Monitoring System (NARMS). NARMS monitors the potential for antimicrobial resistance in bacteria found in food production and within humans. The group guides the federal scientific research and policies on antimicrobial resistance.

Within the FDA, the Center for Veterinary Medicine (CVM) is specifically responsible for the surveillance of drug use in animal production and the approval of new animal drugs (FDA, 2014b). Patterns in bacterial resistance provide a base risk analysis to new drugs, which strongly assists the CVM in the new drug approval process. In addition, the monitoring system functions to recognize developing bacterial resistance threats in order to devise response strategies to slowly increasing resistance (FDA, 2016c,d).

To further monitor the degree to which antibiotics were present in food, specifically seafood, the FDA began to consistently analyze produced food. Recurrent testing for drug residues in seafood was not performed until 2002 when the FDA implemented the Chemotherapeutics in Seafood Compliance Program (CSCP) (FDA, 2015d). The program was developed to create a sample inventory of seafood from different domestic and international locations and examine them for unapproved drug residues (FDA, 2015d).

In the same year, the Animal Drug Availability Act (ADAA) was passed to expedite the approval and sales of new animal production drugs. Recognizing that some drugs should be more closely monitored than others, the veterinary feed drug (VFD) classification was created. This classification was strictly for new drugs that were developed to support animal development and must be issued under the approval of a veterinarian, indicating that the FDA has been concerned about bacterial resistance (FDA, 2015). These drugs must be blended with water or feed and cannot be administered in other fashion (Veterinary Feed

Directive, 2015). These feeds may also have one or more drugs within them (FDA, 2015g FDA, 2015g).

In 2000, the FDA passed a final rule that required all VFD drugs to require a VFD order. The order obtained required key information about the producer and in doing so created a stronger structure for the purchase of veterinary feed drugs. This ruling made the traceability of antibiotic distribution more practical, but only for the handful of newly introduced VFDs (Veterinary Feed Directive, 2015).

Since then, the FDA has issued two documents detailing non-mandatory guidelines advising antibiotic manufacturers and veterinarians on how they should address bacterial resistance. Guidance #209 was issued in 2012 by the FDA to declare what their position was on the proper and improper use conditions of antibiotics for animals (FDA, 2012). The guidance focused on medically important drugs and drugs acknowledged as beneficial for production uses. This stated that medically important drugs should be limited for use in animal development and should only be strictly used. The guidance laid the groundwork for a more concrete guidance framework that was issued one year later (FDA, 2012).

In 2013, the FDA introduced guidance #213, which was a framework suggesting a voluntary effort over a three-year span, to gradually phase in safer adjustments to how medically important antibacterial drugs are advertised and applied in animal production operations. It was developed for use in tandem with insight from guidance #209 (FDA, 2014a). The guidance called for animal antibiotic manufacturers to remove the indication of production aides from the label of their drug. Once manufacturers did this, it would then be illegal for producers to administer the antibiotic to their animals unless for therapeutic,

medical issues, rather than enhanced production. Prior to this guidance, no effort was made to address antibiotic overuse use in animal development (Elgin & Martin, Bloomberg, 2014).

The second recommendation from guidance #213 was to limit free access to animal antibiotics by removing then as over the counter pharmaceuticals (FDA, 2013a). The guidance urged for the inclusion of a veterinarian in the acquisition process of all medically important drugs. The veterinarian would assess the need for the application of the antibiotic, as well as the most effective dosage. The decision to provide the producer access to the antibiotic would first be contingent on the drugs effectiveness towards the diagnosed infection. Access to drugs for preventative use is advised to be under the veterinarian's jurisdiction (FDA, 2013a). This change would address the loophole mentioned previously, as the producer's freedom to apply antibiotics would be restricted. Lastly, alternatives to drug use were suggested to be explored by veterinarians before requests are fulfilled. The veterinarian would then issue a prescription to the producer that would be required by the drug manufacturer to sell the producer any antibiotics. It is intended that the veterinarian and the need for a prescription would limit the inappropriate, overuse of antibiotics (FDA, 2013b).

3.3 The Veterinary Feed Directive and Current Regulatory Environment

In 2015, the FDA legally mandated their recommendations introduced from their previous two guidances by introducing legislation to restrict the use of antibiotics for medicinal uses, such as disease and infection defense, making it illegal to use drugs for production enhancement. The Veterinary Feed Directive (VFD) final rule is the most recent action by the FDA to curb the spread and rapid progression of bacterial resistance. The goal of the rule is to reduce inappropriate overuse of antibiotic drugs in animal production (Veterinary Feed

Directive, 2015). As of January 1, 2017, all medically important antibiotics in animal feed are now classified as veterinary feed drugs (VFD), requiring VFD orders for all medically important drugs (FDA, 2015g). It is now illegal for antibiotic manufacturers to advertise a drug as useful for production purposes. The FDA is only focusing on drugs that are used for animals and for humans rather than on antibiotics used solely for animals. The Veterinary Feed Directive, final rule is essentially a mandating finalization of guidance's #209 and #213.

Similar to before the Veterinary Feed Directive final rule, veterinarians will need to authorize the sales of veterinary feed drugs to producers. The producer must first submit a VFD order form requesting the drug and provide sufficient evidence of a need for that drug (FDA, 2015g;Veterinary Feed Directive, 2015). However, prior to the rule, only VFD drugs required a prescription from a veterinarian and only a few drugs were classified as veterinary feed drugs because when the classification was introduced, special requirements were only instituted for new animal drugs. Under the VFD final rule, all medically important drugs will be classified as VFD drugs and all medically important veterinary feed drugs that were previously available over the counter will now require a prescription through a VFD order (FDA, 2015g).

The VFD rule also equips veterinarians with a framework to determine the safest and most efficient use of antibiotics (Veterinary Feed Directive, 2015). The rule clarifies the responsibilities of the veterinarian, the producer, and the distributor and highlights new, stronger requirements for veterinarians and producers, referred to as the Veterinarian Client Patient Relationship (VCPR) (FDA, 2015g). Clearer coordination and open information sharing are highlighted as the core of VCPR's. This includes a physical examination of the

animal and protocol to provide follow-up examinations (Veterinary Feed Directive, 2015) Veterinarians are advised under the final rule to identify a specific disease, dosage, and duration before administering access to antibiotics (FDA, 2015g). Each state may have their own individual set of VCPR requirements but must accommodate the blanket set of national requirements defined by the Veterinary Feed Directive (VFD) final rule (FDA, 2015g).

FDA intends to continue its partnership with the USDA and the CDC to develop a more accurate and inclusive database of antibiotic sales and application in the U.S. This information will be useful in helping the FDA gauge the effectiveness of the VFD. Additionally, when conjoined with research from NARMS, antibiotic use and bacterial resistance trends can be better monitored and assessed (FDA, 2015g).

3.4 Conclusion

The FDA hopes to reduce the excessive use of antibiotics in animal production and overall to slow the spread of resistant bacteria. A restrictive system like this evokes concern for producers who develop their animals in confined feeding operations and have been using antibiotics regularly for years. The VFD was a significant step towards slowing resistance, especially due to the large amount used in the U.S. not only in aquaculture but in animal production as well. Although the FDA has been active in addressing antibiotic use domestically, a significant portion of all seafood consumed in the U.S. is imported. Because there are far fewer production regulations in the countries that import seafood to the U.S., it is highly likely that antibiotics are in frequent use in many foreign aquaculture operations. As a result, because so much seafood is imported with potentially resistant bacteria, efforts by the FDA will ultimately be undermined. Because the FDA's efforts effectively target

domestic beef and poultry, the heavy effect of seafood drug use by importers is not accounted for. In the following three chapters, evidence is presented from the importation of shrimp, salmon and tilapia illustrating potential risks associated with this lack of accounting.

Chapter IV: Shrimp

4.1 Introduction

In 2016, the U.S. imported 6.1 billion pounds of seafood (Table 4.1). Shrimp, which is also the most consumed seafood accounted for 21.7% of those 2016 seafood imports to the U.S. (NOAA, 2016). In 2015, the U.S. produced only 3.27 million pounds of shrimp, compared to 1.3 billion pounds of shrimp, which was imported in the same year (NOAA-NMFS, 2015, 2017). Antibiotic use is particularly common in shrimp aquaculture due to the growth conditions the organisms are subject to. According to an international antimicrobial survey, Tuševljak et al., (2013) found that shrimp was most often cited to have maintained bacteria that exhibited resistance across all classes of antimicrobials, indicating a wide range of drug use in shrimp production. As shown in table 4.1 India and Indonesia are the top shrimp-producing exporters to the U.S., accounting for 25.4% and 19.4% of all shrimp imported. This chapter will focus specifically on the aquaculture operations and regulations of these two countries, relative to shrimp.

Table 4.1: U.S. Shrimp Imports in 2016 (source: NOAA, National Marine Fisheries Service-U.S. shrimp import totals by country)

Rank	Country	Pounds	Percentage
1	India	339,478,014	25.4%
2	Indonesia	258,161,946	19.4%
3	Thailand	181,194,542	13.5%
4	Ecuador	161,422,898	12.1%
5	Vietnam	140,331,086	10.5%
6	China	77,028,403	5.7%
7	Mexico	55,835,454	4.1%
8	Canada	8,647,244	<1%
9	Honduras	8,040,911	<1%
10	Malaysia	611,183	<1%
	Total:	**1,230,751,681**	92%
	All other countries:	103,186,204	8%
Total	Shrimp Imports 2016:	**1,333,937,885**	

4.2 Production Process

Shrimp aquaculture is a low-cost, highly profitable, rural industry prominent in India and Indonesia (Nawaz et al., 2015). In both countries, Whiteleg shrimp (*Litopenaeus vannamei*) and the Giant Tiger Prawn (*Penaeus monodon*) are the predominant shrimp species produced. In 2014, two-thirds of Indonesian shrimp production was whiteleg shrimp. White leg shrimp was introduced in the early 2000's to Indonesia and soon after to India. In India, whiteleg shrimp production increased from 1,731 metric tons to 81,000 metric tons from 2010-2012 and has been increasing steadily each year. In the same years, by comparison, Indian giant tiger prawn production increased from 119,000 metric tons to 136,000 metric tons (Thompson, 2015; Ma, 2015; CAA 2012). In 2014, Indonesia produced 411,700 metric tons of whiteleg shrimp, exceeding production of giant tiger prawn, which yielded 126, 600 metric tons.

Shrimp farming methods are similar in India and Indonesia. In India, shrimp farming generally uses a pond-based enclosure with brackish water as the main water type. Indonesia slightly differs in that their newer developed ponds use concrete or polyethylene lining, which is effective in reducing erosion and sedimentation (Taw, 2005). However, both countries use intensive aquaculture practices.

There are two primary production system types in India and Indonesia, extensive and intensive production (Yi et al., 2009). Extensive production describes low-density, low-input production operations on farms that are generally less than 2 hectares in size. In turn, this production type requires a less demanding water exchange rate compared to other practices, but also yields the lowest amount of product (Yi et al., 2009). Giant tiger prawn production is primarily done in extensive operations. Comparatively, greater shrimp densities and larger

amounts of inputs in ponds characterize intensive shrimp farming. Some intensive farms range from 5 to100 hectares in size, though most whiteleg shrimp farms in Indonesia are on average 10 hectares (Yi et al., 2009). Generally within each large farm there are smaller ponds. Additionally, shrimp densities within the ponds normally exceed 100 shrimp per square meter. The life span of this shrimp species is on average three to four months (Thompson, 2015). In these settings, shrimp are exposed to not only high-stress levels but also a high susceptibility to disease as they are confined in an enclosed pond and reside in fecal matter and other biological pathogens that exist in the pond. This threat encourages farmers to use antibiotics to prevent disease.

The popularity among farmers of the whiteleg shrimp compared to the giant tiger prawn is largely due to the greater production efficiency of the whiteleg shrimp (Yi et al. 2009). The giant tiger prawn thrives best in extensive production systems, where the whiteleg shrimp can persist and thrive in a more confined setting (Yi et al., 2009). However, whiteleg shrimp production requires a higher daily exchange rate of the farm's pond water. Daily exchange rates represent the percentage of water that is replaced within the pond with fresh water in order to mediate the salinity and contaminant concentration in the production ponds. To address this, producers withdraw water from the ponds and replace it with fresh water. Common daily exchange rates range for intensive ponds range from 5% to 25% (Jory and Cabrera 2012). Compared to giant tiger prawn production, which is performed in an extensive setting and has a recommended daily exchange rate of 10 %. Practically all whiteleg shrimp producers use pumps and aerators to maintain suitable pond water quality and minimize stressors, in addition to prophylactic antibiotics (Thompson, 2015; Ma, 2015).

Shrimp production practices lead to environmental degradation in two particular

ways. First, production ponds have historically been constructed in previous mangroves and near coastlines. As a result of this, shrimp production is directly connected to the transition of ecologically important mangrove areas. According to Ilman et al. (2011), shrimp aquaculture industry is the primary reason for the removal of 750,000 ha of mangrove forests in Indonesia. Similar mangrove degradation trends have been evident in Indian coastal regions as well (Thompson, 2015). Second, because producers must remove and release nutrient- and pathogen-contaminated water to introduce fresh water into the ponds, there are concerns of effluent discharge that could negatively interact with the proximate environment. This production system literally submerses shrimp into a pathogen-dense environment, which creates an extremely stressful and pathogenic environment for shrimp to develop in. Furthermore, a lack of clean water needed to filter through shrimp ponds may also encourage producers to depend more heavily on antibiotic use.

4.3 Regulatory Process

Each country has a governing body that overlooks domestic aquaculture production and distribution to some degree. These agencies can play a vital role in shaping the norms of production within their country. Governing authorities in this respect can impact the quality and threat of seafood that is exported to consumers all over the world. A country's regulatory process in relation to aquaculture production may encapsulate food and health safety standards along all steps of the supply chain. However, the degree in which foreign agencies enforce and even interact with their aquaculture industry differ for various reasons.

4.3.1 India

The Coastal Aquaculture Authority, the Marine Products Export Development Authority

(MPEDA), and the Export Inspection Council are the key bodies in India that monitor the use of antibiotics in shrimp farming as well as shrimp products prior to export. The Export Inspection Council was created in 1963 to strengthen quality assurance and inspection protocol for all exports (EIC, 2016). The council establishes standards for domestic inspection and quality control. MPEDA was first instituted in 1972 to facilitate trade, production, and export of Indian seafood (MPEDA, 2016). Their responsibilities grew to include aquaculture as it became more prominent in India. In 2005, The Coastal Aquaculture Authority (CAA) was created under the Coastal Aquaculture Authority Act mandating government management of coastal aquaculture to ensure that aquaculture practices do not harm the coastal environment and do not impair the livelihoods of people residing in the coastal areas (CAA, 2005). The agency monitors all coastal aquaculture farms and regulates their operations including their inputs. The CAA manages coastal zones by mandating rules to address impacts on pond siting.

In regards to shrimp aquaculture, the CAA requires all shrimp operations to register their company with the agency, which is then subject to inspection (CAA, 2012). Although information on inspection statistics is unavailable, the CAA has a list of 20 banned substances and 4 approved substances for shrimp aquaculture. Tetracycline[2], oxytetracycline, trimethoprim & oxolinic acid are allowed in shrimp production but must not exceed pre-established, Maximum Permissible Residual Levels (MRL) (CAA, 2012) The MPEDA requires evidence of testing done on all exports for antibiotic residues on farmed shrimp from all registered farms. Shrimp farms in India are generally small. In India, since 2005, 22,000 newly registered shrimp farms were less than 2 hectares. However, there is evidence of

[2] Refer to Appendix for description of all drugs mentioned in this research.

frequent occurrence of illegal shrimp farms in India. In one example from 2015, the CAA closed down 3500 hectares of farmland comprised of 100 illegal shrimp farms (Kearns 2015).

Regulations by the CAA were created in 2009 specifically for Indian whiteleg shrimp production (Thompson, 2015). The regulation mandated that farms must be securely enclosed to avoid escape and so unwanted species do not enter. It is also mandated that ponds have an intake reservoir as well as a holding reservoir so that water can be held and chlorinated before being released if ever there were a disease outbreak within the pond (Thompson, 2015). If a breakout is not recognized, farmers are not required to chlorinate the pond water before releasing it. CAA regulations require producers to be able to hold their exchange water in a reservoir for up to two days during chlorination (Thompson, 2015). In other words producers are not mandated to chlorinate removed water after each use.

In efforts to address environmental degradation, in India, a site inspection must be performed by the CAA in order to register a whiteleg shrimp farm (Ministry of Agriculture, 2012). All farms regardless of intent to export or sell domestically are required to register their operation with the CAA. Because shrimp production has been the leading cause of coastal erosion and mangrove destruction in India, the CAA made it illegal for farms to be sited less than 200 meters from the high tide line (CAA 2012). An environmental impact assessment (EIA) is mandatory for farms larger than 40 hectares. However, as mentioned, since 2005, over 80% (2000) of newly registered farms were less than 2 hectares, meaning the lack of need for an environmental assessment (Thompson, 2015).

India has banned several classes of antibiotic drugs in aquaculture. Antibiotics belong to specific classes and have many different molecular variations of that drug that fall

within that class. India has banned most drugs from the class: nitrofurans, sulfones, nitroimidazoles, quinolones, sulfanomides, and amphenicols (CAA, 2012). However, India prohibits the use of oxytetracycline, which is a tetracycline, trimethoprim, a sulfanomide and oxolinic acid, a quinolone. The maximum residual levels permitted for the use of these drugs in shrimp in India are 0.1 ppm, 0.1 ppm, 0.05 ppm, 0.3 ppm. The U.S. has approved the use of oxytetracycline and tetracycline for aquaculture but only for finfish, not shrimp, and the U.S. M.R.L for both these two drugs is 2 ppm. Interestingly, this M.R.L is not as stringent as India's 0.1 ppm residue threshold. Additionally, trimethoprim, and oxolinic acid are not approved for use by the FDA but are approved in India (FDA, 2015, CAA, 2012). According to the World Organization for animal health (OIE), oxytetracycline and trimethoprim are "critically important" antimicrobials, and oxolinic acid is considered a "highly important" antibiotic.

4.3.2 Indonesia

In Indonesia, the Ministry of Marine Affairs and Fisheries (DKP) is the main fishery authority. The Directorate-General of Aquaculture Development works in tandem with the DKP to manage all catch and farm fish operation in the country (National Aquaculture Legislation Overview, 2006). In 1999 there was a certification system created in Indonesia for chemicals important for agriculture, but no system was introduced for aquaculture drugs (NALO, 2006). In 2004, Fisheries Law No. 31/2004 was instituted to promote operational safety and proper, sustainable fishery procedures, however Indonesia's national drug and chemical regulations for aquaculture are not well defined. The Fisheries Law No.31 of 2004 does not directly list banned or approved drugs for aquaculture. The extent of mention of

harmful substances is that they must not cause harm to aquatic resources. There is no specific mention of antibiotics or resistance (NALO, 2006). Lastly, Indonesia differs from India in terms of environmental assessment in that only farms larger than 50 hectares are required to have an environmental assessment performed (Phillips et al. 2009).

4.4.3 Regulatory Comparison between India & Indonesia

Compared to India, Indonesian authorities are behind in terms of regulations to address the use of drugs in aquaculture. India has a list in place of approved and banned aquaculture substances where Indonesia does not. However, producers in both India and Indonesia have unrestricted access to antibiotics, not requiring the oversight of a veterinarian for drug purchase, although, for approved antimicrobials, India has determined M.R.L's for each drug. This again differs from Indonesia, which does not. Based on the regulatory framework and mandates in place by these two countries, it would seem that the Indian government has been more responsive to bacterial antibiotic resistance than that of Indonesia.

4.4 Inspection Violations & Reports of Antibiotic Use

There are a few ways antibiotic use is identified in aquaculture production. First, farmed seafood samples can be chemically analyzed for drug residues. Second, bacteria on the sample or proximate to the aquaculture site can be tested for resistance to different drugs. This is usually done through private certifiers contracted by the U.S., by the FDA upon arrival to the U.S. or by scientific researchers. If a bacterium is resistant to the effect of a drug it is reason to assume that the drug has been used in excess at low doses proximate to

where the bacteria are found.

In two separate studies from 2016 by Stalin & Srinivasan, three multi-resistant bacterial strains were isolated in Indian shrimp farm sediments that each showed resistance to four different antibiotics (Stalin & Srinivasan, 2016a,b). The significance of identifying multi-drug resistant bacteria in and near shrimp farms is that it provides information to the specific type of drugs used at the site. Moreover, frequently recognized resistance to a specific antibiotic speaks to the frequency of use in that region. Although it represents a very small sample, it does imply that there are likely to be some instances of antibiotic resistance risks associated with Indian shrimp production.

Significant shipments of Indian shrimp have been rejected for evidence of drug residues. In 2016, the U.S. rejected 114 lines of shrimp from Indian exporters for a variety of violations, including drug residues. Each line generally refers to a shipping container, containing between 36,000 – 40,000 pounds (Hindu Business Line, 2015). Of those rejected lines, 95 were rejected for the presence of a drug. The 95 line rejections are comprised of violations for containing unknown veterinary drugs and/or nitrofurans in the imported shrimp. Of the drug-based rejections, 69 lines were rejected due to unidentified veterinary drugs alone; if a drug residue is not identifiable by the FDA it is otherwise illegal for use. 21 lines were rejected due to the physical identification of drug residues of the nitrofuran class, in the shrimp along with other unidentified drugs (FDA, import refusal data, 2017). The remaining line rejections were due to the presence of salmonella or filth on the shrimp import.

Although there were multiple rejections by the U.S. of shrimp from Indonesia in 2016, there were none specifically for violations of antibiotic residues. Instead, Indonesian-

sourced shrimp rejections were a result of salmonella identification and filth contaminants in the shipment. In 2015, the U.S. instituted import alerts for specific Indonesian producers as multiple shipments exhibited residues of nitrofurans and enrofloxacin (FDA, IRD, 2017). This means that all further exports from those specifically identified exporters must be physically inspected before entry into the U.S. until the import alert is retracted.

Evidence that contaminated Indonesian-sourced shrimp is entering US retail markets was found in 2015. Testing samples purchased in the U.S. and chemically analyzed for the presence of antibiotic residues, sulfadimethoxine residues were identified in Indonesian shrimp. This antibiotic is not approved for shrimp production in the U.S. (Done & Halden, 2015). Therefore, acknowledging the amount of shrimp that is imported annually, it is highly likely that antibiotic contaminated shrimp does indeed make its way to consumers in the U.S.

4.5 Implications for Antibiotic Contaminants in U.S. Consumer Shrimp Supply

In 2016, shrimp shipments from India were rejected due to the presence of nitrofuran residues. Similarly, in 2015 shrimp shipments from Indonesia were rejected because of the identification of nitrofuran and enrofloxacin residues. Although India appears to have a relatively stringently regulated aquaculture system they still received more shrimp violations than any other country in 2016 (FDA, IRD, 2017). Moreover, the rejections were due to the presence of drugs that were supposed to be banned in India. Indonesia conversely, does not have a list of banned nor approved antibiotic drugs. From both these countries, recent instances of discovered antibiotic use indicate that there are undoubtedly some gaps in governance over shrimp farming in both India and Indonesia posing health risks to U.S. consumers.

Chapter V: Salmon

5.1 Introduction

Salmon is the third most popular seafood type in the U.S. In 2016 the U.S. imported 778,429,685 pounds of salmon, which accounted for 12.7% of all seafood imported by weight, 80% of which was Atlantic salmon (Table 5.1; NOAA, 2016). Two hundred and eighty million pounds of farmed Atlantic salmon was sourced from Chile and 192 million pounds from Canada in 2016. Chile and Canada are major producers of Atlantic salmon and account for large portions of our salmon imports. In 2016, Chile accounted for 37.2% and Canada for 28.3% of all salmon to enter the U.S. (Table 5.1; NOAA, 2017). Given the importance of Chile and Canada as exporters of salmon to the U.S., this review will focus on how these two countries regulate the use of antibiotics in salmon farming systems and evidence of contamination in imports reaching the U.S.

Table 5.1 – U.S. Salmon Imports in 2016 (source: NOAA, National Marine Fisheries Service)

Rank	**Country**	**Pounds**	**Percentage**
1	Chile	289,428,898	37.2%
2	Canada	220,391,445	28.3%
3	China	85,789,051	11%
4	Faroe Islands	32,128,959	4.1%
5	Norway	7,941,533	1%
	Total:	**635,679,886**	81.6%
	All other countries:	142,749,799	18.4%
Total	Salmon import 2016:	**778,429,685**	

5.2 Production Process

Atlantic salmon (*Salmo salar*) is the most commonly produced salmon type in aquaculture systems in Chile and Canada (Brisdon, 2014a). In both locations, the fish are grown in floating net pens or cages in the ocean off their respective country's coasts. Net pens are

generally circular and range from 50-150 meters in diameter and 15 meters deep (Brisdon, 2014a). Atlantic salmon is actually not native to Chile but is to Canada. Typically, salmon produced in these settings are susceptible to infection by pathogens and parasites from the open sea and nearby farms (Rimstad 2011). Because Atlantic salmon is native to Canada, there is a concern of pathogens in farms infecting the wild population of salmon, an issue not experienced in Chile. In Chile, Salmon Rickettsial Syndrome (SRS) is the most common disease that threatens salmon and warrants the use of antibiotics (Brisdon, 2014a).

Salmon production in Chile differs from Canada due to the high densities of fish in production areas, which enhance the likelihood of disease transmission. In Chile, farms are located very close to each other and salmon are held in very high densities in individual nets which allows for a greater potential for wastes to interact and transfer pathogens and other microbial material (Buschmann et al. 2007). Chilean salmon are held in open nets in average densities between 55-66 pounds of fish per cubic meter (Alvial et al., 2012). Canadian Atlantic salmon is typically held in open nets in densities that average between 17 – 39 pounds per cubic meter (Watershed Watch Salmon Society, 2004). Juvenile salmon are held in hatcheries until they smolt and are placed into nets. Upon entry into open nets, salmon usually weigh less than 1 pound. When they are ready for harvest they usually weigh between 4 and 13 pounds and are grown for 18 to 24 months before harvest (Voorhees, 2016).

In floating net salmon farming, nutrients and organic compounds including unconsumed feed and fecal matter are transported by currents or enrich the sediments below or near the net. This can result in algal blooms that can impair the health of an aquatic ecosystem. Additionally, in undigested fish feed and feces, antibiotic metabolites may still

remain in sediments and may accumulate over time (Brisdon, 2014a). This issue is similar in both Chile and Canada except due to enforced regulation in Canada, salmon aquaculture operations are less dense in terms of single net and in terms of proximity of farms than in Chile. This means that all together, there is less of an accumulation of bacteria and nutrients to interfere with the normal hydrologic chemistry in the sea, as well as significantly less antibiotic use in Canada compared to Chile.

5.3 Regulatory Process

5.3.1 Chile

Chile's fishery and aquaculture regulatory bodies are Subpesca (undersecretary of fisheries) and Sernapesca, Chile's National Fisheries and Aquaculture Service. Subpesca was created in 2010 to better manage the country's aquaculture industry and to enhance the country's export inspection efficacy and overall enforcement (Alvial et al., 2012). Prior to shipment, all fishery products must be first authorized by Sernapesca. This is generally a notification to the agency so that Sernapesca can assess the product, destination, and other required certifications requested by the importing country. There is an optional quality assurance program that aquaculture producers can take part in to be eligible for a national sanitary certification requirement that would make their production source more attractive to foreign importers (Brisdon, 2014a). Additionally, for registered aquaculture farms, producers are capable of receiving a declaration of origin certificate that may also make them appear more attractive to importers.

Chile's Ministry of Agriculture Law No. 19283, passed in 1995 addresses concerns and proper management of veterinary drugs. However, this law only regulates the use of

antibiotics in terrestrial agriculture and not aquaculture (Brisdon, 2014a). Antibiotic use in aquaculture is not regulated in Chile; there are no explicitly banned veterinary drugs, and unlimited amounts of antibiotics can easily be obtained from manufacturers. Moreover, according to Niklitschek et al. 2013, Chile's salmon industry primarily uses six antibiotics: oxolinic acid, amoxicillin, erythromycin, flumequine, florfenicol and oxytetracycline, all of which are considered medically important.

In terms of environmental impact, benthic nutrient enrichment is relevant to this fish farming type simply due to the floating net design. In 2010, Chile instituted changes to their environmental regulations for aquaculture by instituting measures to include monitoring of sediments below farms. However, according to Quiroga et al. (2013), the regulatory bodies of Chile have not yet devised an effective monitoring and evaluation system to address the environmental impact of benthic sediment enrichment. Moreover, as there are no regulations on antibiotic use in Chile, there are in effect no federal measures to assess the effect excess antibiotics are having on the marine environment in Chile. Because large quantities of salmon consumed in the U.S. originate from Chilean waters, where excess antibiotic use is common, it is highly likely that antibiotic residues exist in a robust amount of imports.

5.3.2 Canada

In Canada, exported seafood is regulated by the Canadian Food Inspection Agency (CFIA) (CFIA, 2014). The CFIA registers all fish-processing facilities and farming operations. The agency also performs facility and product inspections of registered producers, examining fish products for pathogens, chemicals, and residues (Brisdon, 2014b). Canada has a similar Hazard Analysis and Critical Control Points (HACCP) plan, much like the U.S. The plan

emphasizes prevention protocol for producers to avoid chemical or safety hazards. In addition, all exporters must develop a Quality Management Program (QMP) that is also federally evaluated to ensure the production methods are in line with safety standards of importing countries (Brisdon, 2014b).

Canadian aquaculture regulation differs from Chile in three main ways. First, antimicrobial drugs can only be obtained after receiving a veterinary prescription. Second, it is illegal to use the drug as a prophylactic, and third, all usage must be reported the Canadian Department of Fisheries (DOF). The Canadian Department of Fisheries has approved eight drugs for use in salmon aquaculture and has been monitoring domestic antibiotic since 1995 (Morrison & Skasida, 2013), however Canada has more approved antibiotic drugs than the U.S. Both the U.S. and Canada have approved florfenicol, oxytetracycline, ormetoprim, sulfadimethoxine and teflubenzuron veterinary medicines for animal feed all with similar M.R.L's. Canada, however, has also approved trimethoprim and sulfadiazine, all with MRL's less than 0.3 ppm and both of which are critically important medicinal drugs. The impacts of top-down efforts in Canada to reduce antibiotic use have been substantial. From 1995 to 2009, the Canadian salmon industry reportedly reduced its total antimicrobial use by 87.5% (Morrison & Saksida, 2013). Finally, for salmon aquaculture to take place in Canada, producers must first obtain licenses from the governing marine agency in their province (Brisdon, 2014b). However, this is not a uniform requirement. Interestingly, not all provinces require an environmental impact assessment prior to siting an operation. For example, the New Brunswick and Newfoundland Provinces require an EIS, where siting in the Nova Scotia Province does not.

5.3.3 Regulatory Comparison between Chile & Canada

Aquaculture regulation in Chile and Canada differ substantially. Chile has weak regulation enforcement and has no direct regulatory mandates in place to specifically address antibiotic usage. Canada on the other hand has a regulatory system similar to the U.S.'s Veterinary Feed Directive, which restricts producer accessibility to antibiotics. In addition to having a set list of banned and approved aquaculture drugs, for salmon farmers to obtain antibiotics they must seek veterinarian assistance. Although Canada and Chile's operational design are similar, their governing authorities differ in regimenting the use of medically important drugs in their respective country. It is important when drug application practices are regulated in a country that exports its products because it adds an additional layer of assurance through regulation and inspection in regards to safety for the importing country. Based on the regulatory statues alone, we would expect to find a greater degree of contamination in both antibiotic residue and in antibiotic-resistant organisms on salmon imported from Chile.

5.4 Inspection Violations & Reports of Antibiotic Use

In Chile, oxolinic acid, amoxicillin, erythromycin, flumequine, florfenicol, and oxytetracycline were identified as the most commonly used antibiotics all of which are classified by the World Organization for Animal health as either critically or highly important (Brisdon, 2014, 2017; OIE, 2015). In a study from 2012, traces of the antimicrobial flumequine were isolated from sediments below Chilean salmon farms and bacteria also obtained from the same locations were found to be resistant to oxytetracycline, oxolinic acid, and florfenicol (Buschmann et al., 2012).

Although there have been multiple rejections from Canada and Chile for salmon in

2016, there were no rejections on the basis of antibiotic evidence. Instead, the rejections for these countries were due to cases of salmonella contamination of the product and/or bacterial contamination, coded as 'Filth" by the FDA (FDA, IRD, 2017). In a study where farmed salmon sourced from both Canada and Chile were purchased in the U.S., oxytetracycline was the only drug residue found in both samples. Oxytetracycline is approved for use by the FDA for aquaculture production, however, the residual concentration for oxytetracycline must remain under 2 ppm, a standard which was met in both cases (Done & Halden, 2015). Interestingly, Canada also has a lower MRL for oxytetracycline compared the U.S., the maximum residual concentration for that drug in Canada is 0.2 ppm.

5.5 Implications for Antibiotic Contaminants in U.S. Consumer Salmon Supply

Chile and Canada offer two polarizing approaches toward aquaculture regulation, with respect to antibiotic resistance. Chile has minimal regulations on antibiotic usage and has no specifically banned aquaculture drugs. Conversely, Canada has a veterinary drug system identical to the one the U.S. has recently adopted. Furthermore, Canada uses significantly fewer antibiotics in production annually then Chile. The frequent use of these drugs in Chile is supported not only by data from Sernapesca, but also by the identification of bacteria that are resistant to multiple of the mentioned medically important drugs. For that reason, salmon from Chile appear more threating than salmon sourced from Canada. However, shipments rejections by the U.S. do not indicate excessive or illegal drug use by either country. The caveat here is that the U.S. does have a very low import inspection rate, which could potentially explain the lack of shipment rejections. Still however, in spite of the low standards in Chile, we are not seeing evidence of antibiotic resistance in imports of salmon.

Chapter VI: Tilapia

6.1 Introduction

According to NOAA, tilapia is the fourth most consumed fish in the U.S. (National Fisheries Institute, 2015). In 2016 the U.S. imported 434 million pounds of tilapia, which accounted for about 7% of all seafood imports that year (Table 6.1). Latest available information indicates the U.S. produced only 145,163 pounds of tilapia in 2015. China was the source of 73.6% of all U.S. tilapia imports in 2016 (Table 6.1). In addition to producing the most aquaculture globally, China accounts for 36% of all tilapia produced (FAO 2015). The remainder of this chapter will focus specifically on China as they are accountable for the vast majority of the tilapia consumed in the U.S.

Table 6.1 – U.S. Tilapia Imports in 2016 (source: NOAA, National Marine Fisheries Service)

Rank	Country	Pounds	Percentage
1	China	320,203,935	73.6%
2	Taiwan	27,519,234	6.3%
3	Honduras	20,273,220	4.7%
4	Indonesia	17,055,818	3.9%
5	Columbia	12,032,387	2.8%
	Total:	**397,084,594**	91.3%
	All other countries:	37,753,913	8.7%
Total	Tilapia Imports 2016:	**434,838,507**	

6.2 Production Process

Nile Tilapia (*Oreochromis niloticus*) is primarily farmed in southern China. It is native to the tropics and thrives in warmer waters, and temperatures under 50°F is uninhabitable for tilapia (Sifa et al. 2002). Less than 10% of tilapia is farmed in northern China with waters warmed by nearby power plants. Interestingly, tilapia can persist in either fresh or salt water and are omnivores (Fitzsimmons and Watanabem, 2010). Tilapia can be nurtured to grow on very

little feed but for production purposes are generally provided excess feed inputs that go unconsumed by the fish and contribute to effluent outputs. Tilapia, unlike salmon, reside in closed ponds, so their biological wastes are held until released. Ponds are on average between 0.5 and 2 ha (Seafood Trade Intelligence, 2016). This creates a dangerous, pathogenic environment for developing tilapia. After 2-3 months in a small nursery pond or tank, tilapia then are grown to their harvest weight for 5-6 months (Rakocy, 2005). Information regarding tilapia stock density in China is unavailable, however, tilapia production in Thailand is similar to that in China and serve as a proxy. In Thailand, tilapia are stocked at 1-3 fish per square meter (Sarnissa, 2016). Only during harvest do tilapia ponds exchange water. Furthermore, farms often release their wastewater without any form of treatment, posing a threat to the environment and wild fish species (Zajdband, 2012).

There are two common methods used in China for farming tilapia. “Integrated farming” produces fish in medium sized ponds and utilizes terrestrial livestock manure as fertilizer. “Specialized farming” focuses on tilapia and is either grown in a mono or polyculture (Zajdband, 2012). When in a polyculture, tilapia are also often farmed with carp. Carp are helpful in these aquaculture settings in that they help to reduce the nitrogen load within the pond. Because carp are filter feeders they remove greater amounts of phytoplankton and zooplankton from the pond than tilapia can alone (Turker et al. 2003). In a setting such as this, the proportion of tilapia to carp ranges from 90% to 10%. Most Chinese tilapia ponds discharge once a harvest and therefore the presence of nitrogen reducing species is beneficial (Xiao et al. 2010).

6.3 Regulatory Process - China

In regards to veterinary drugs, the Chinese Ministry of Agriculture has banned several

medically important antibiotics for aquaculture use and has developed minimal residual levels for the antibiotics that they have approved (Zajdband, 2012). The purchase of antibiotics for livestock requires a veterinary prescription, however this is not enforced. Moreover, aquaculture producers can purchase antibiotics without the need for a prescription (Zajdband, 2012).

In terms of regulation, China has approved thirteen specific aquaculture drugs; enrofloxacin, florfenicol, flumequine, neomycin, norfloxacin, oxolinic acid, sulfadiazine, sulfamethazine, sulfamethoxazole, doxycycline sulfamonomethoxine, thiamphenicol, and trimethoprim. Of these, only florfenicol and sulfamonomethoxine are approved for use in the U.S. Unfortunately, Chinese government data showing the exact amount of antibiotics used in aquaculture activities is unavailable. China has however, banned the use of amoxicillin, chloramphenicol, chlortetracycline, ciprofloxacin, erythromycin, furazolidone, gentamycin, oxytetracycline, penicillin, streptomycin, sulfamerazine, and sulfisoxazole, all of which are medically important in varying degrees.

The Ministry of Agriculture did impose discharge regulations in China for fishponds but only for metals, pesticides, and macronutrients. However, there are no specific regulations to address the discharge of antibiotics present in farm ponds (Zajdband, 2012). In China, wastewater discharge is managed and enforced by local authorities with provincial governments and municipalities responsible for the discharge standards for tilapia farms in their jurisdiction. Regardless of national standards, enforcement is uneven and some areas are likely to have far worse environmental discharge standards than others (NALO, 2012). Moreover, according to Chen et al., 2011, the enforcement of aquaculture discharge regulations are often not enforced primarily because of the role aquaculture plays in local

communities in China, especially if regulations are developed by region (Chen et al. 2011).

6.4 Inspection Violations & Reports of Antibiotic Use

In 2011, Rico et al. (2014) surveyed Chinese tilapia producers to obtain insight on antibiotic use practices. Farmers indicated they commonly used florfenicol, enrofloxacin, and neomycin sulfate in their operations, all of which are medically important. In 2016, the U.S rejected 17 line entries of tilapia from China. However, no rejections were the result of antibiotic residues (FDA, IRD, 2017). The violations were due to pathogenic contamination and unverified shipment documentation. Chinese sourced tilapia purchased in the U.S. was found to have oxytetracycline residues, but at concentrations of less than 1 ppm (Done & Halden, 2015). Although oxytetracycline is banned in China, residues were still isolated in farmed tilapia, indicating illegal drug use even with government regulation in place.

6.5 Implications for Antibiotic Contaminants in U.S. Consumer Tilapia Supply

It is apparent that even though China has banned certain drugs for aquaculture, some are still used in tilapia production. The fact that these drugs are still appearing in aquaculture exports from China indicates that there are gaps in Chinese regulation that allows illegal veterinary drug use on tilapia farms. Gaps in enforcement for this species make it plausible to infer that important veterinary drugs may also be used illegally for animals of different aquaculture operations. Despite reports of drug use and isolated resistant bacteria, the recent lack of import rejections for farmed-Chinese tilapia do not provide strong evidence that antibiotic tainted tilapia are entering the U.S. However, taking into account that so little of U.S. seafood imports are chemically analyzed, it is not irrational to assume antibiotic residues and resistant

bacteria are continuing to enter the U.S. through imported aquaculture.

Chapter VII: Conclusion & Policy Recommendation

In reviewing the relevant peer-reviewed literature and import rejection data of the top seafood exporters to the U.S. it is evident that exposure to antibiotic residues and resistant bacteria are risks presented to American consumers as a result of insufficiently regulated aquaculture imports. Moreover, it seems although some countries have regulations in place to reduce excessive use of antibiotics in aquaculture, they may not be sufficiently enforced. Despite cases of identified resistant bacteria in all production regions, rejection evidence for antibiotic use in shrimp is most prevalent, where evidence for antibiotic use for salmon and tilapia are comparatively weaker. The U.S. physically inspects less than 1% of seafood shipments annually. Because there are shipments that are rejected due to antibiotic residues, it is not implausible to speculate that some antibiotic contaminated seafood is accepted by the U.S. for distribution. Increasing physical inspection rates of imports is an early step the FDA can take to reduce the U.S.'s susceptibility to antibiotic resistance from imported aquaculture.

The E.U. has an approach to handling the risk of antibiotic resistance from imports that differs from that in the U.S. Compared to the U.S., the E.U. inspects at 20% of its imported seafood (Love et al., 2011; Vrignaud, NOAA, 2013). In addition to inspecting greater percentages of their imports, the E.U. has also been more responsive to antimicrobial resistance and have required veterinary prescription for medically important drugs since 2001. Later in 2005, antibiotics were banned as growth promoters for use in animal production, showing a proactive response to antimicrobial resistance a decade earlier than the

U.S. (E.C., 2005). In terms of inspection and antibiotic resistance related to imported aquaculture, the E.U. has been on the forefront.

7.1 Aquaculture Import Regulations in the European Union

Aquaculture importing procedures differ between the U.S. and the E.U. that allow for greater inspection and auditing opportunities of foreign producers. First, for a country to be eligible to export to the E.U., a government agency in the exporting country must be identified and assessed for their reliability to ensure E.U. safety standards within the country of production (European Center for the Promotion of Imports, 2016). Conversely, the FDA does not require the involvement of the exporter's government authority. For the U.S., the exporter's government does not possess a list of individual producers and does not inspect these facilities under FDA safety standards. Moreover, if a producer wants to export seafood to the E.U. they must submit their request for entry through their government authority (C.B.I, 2016). The foreign government agency will then submit an entry form to the E.U's Directorate-General for Health and Consumer Protection requesting entry.

All government agencies that operate in the guidelines of the E.U. must show they have adequate jurisdiction, resources and ability to perform thorough inspections of all stages of the supply chain in their country. Inspections from these authorities include hygiene within the processing plant, as well as the shipping vessels (C.B.I, 2016). E.U import requirements also expect foreign governments to ensure the health of aquaculture species. With this design, the E.U. is able to hold not only the specific exporter but also the foreign agency responsible for the shipments of tainted goods. The foreign governing agency that overlooks these processes in their country is understandably better suited to control and promote safety standards that any other distant agency. The governmental recognition of each exporter

serves as a certification to the E.U. that the production plant has been inspected in the past year and that the production process was carried out as according to HACCP protocol.

The E.U. also performs audits of the governing body in each trading country to assess the effectiveness and control authorities have over enforcing food safety and hygiene standards (Koonse, 2016). E.U. import authorities only accept imports from specific exporters that have been recognized by their government authority and have thus been authorized by E.U. Collectively, through private inspection agencies, the government of the producer, and through the E.U., greater opportunities for inspection exist. Although private inspection companies inspect some exporters for the FDA, there are shipments that enter the U.S. without any private or government safety certifications.

In terms of directly responding to antimicrobial resistance, the E.U. introduced a five-year action plan in 2011 that emphasized raising surveillance and information sharing between countries (European Commission, 2011). In addition, the action plan introduced campaigns to raise awareness on antibiotic resistance and overuse. A second action plan introduced in 2016 builds on the first and adds focus on strengthening the E.U.'s role among international organization such as the World Health Organization to promote better global management of antibiotics (E.C., 2016).

Promoting research, regulation enforcement, information sharing and education are the primary avenues the E.U. is taking to combat antimicrobial resistance for the duration of the next 5-year plan (E.C, 2016). Though the U.S. has placed focus on monitoring resistance patterns and enhancing inspection there is still a deficiency in inspection rates and capabilities for the U.S. increasing inspection appears to be a fundamental first step to reducing the threat of resistance from imported aquaculture.

7.2 Policy Recommendations

The following recommendations are for the FDA, importers, foreign authorities and organizations that act to curb antibacterial resistance such as the World Health Organization (WHO), the World Organization for Animal Health (OIE) and the Food & Agriculture Organization (FAO).

1. *The FDA should develop stronger relationships with the "competent authorities" of U.S. trade partners and involve them as enforcers of food safety regulation in the trade process.*

Creating coordination with the exporters' governing authority can help the U.S. increase its overall physical inspection of foreign facilities. First, the foreign governing agency will need to agree to inspect production facilities and processes in their country. The U.S. uses third-party certified inspectors abroad and sporadically performs physical facility inspections in foreign countries. By connecting with foreign agencies and making them aware of U.S. drug regulations and safety standards, the U.S. will have assurance from at least the exporting government and the producer that the product was developed with FDA within guidelines. It also indicates that the foreign authority recognizes the producer and has inspected their facility and process. This adds one additional level of assurance to the food production process that is not currently available for the U.S. seafood supply chain. It must be noted that although this, in theory, adds a degree of assurance to food safety, the effectiveness of this is based on the reliability of the exporting country's governing body.

2. *The FDA should increase inspection upon product arrival.*

The U.S. and E.U. inspect imports based on similar criteria. However, compared to the U.S. the E.U. has a greater amount of reception ports as well as a larger budget allocated for import inspection, resulting in greater inspection rates. Neither the E.U. nor the U.S. physically inspects each shipment. Limitations in the U.S. are largely due to lack of funding. However, this constantly growing issue needs much stronger U.S. support and additional fund allocation. Increasing U.S. funding to strengthen the FDA's import inspection affectivity would be costly, but is necessary. Evidence from the E.U. indicates that antibiotic resistance is an issue that will become more costly to address in later years than to combat today. The E.U. already estimates annual costs of €1.5 billion Euros ($1.61 billion USD) attributable to healthcare costs and production losses due to antimicrobial resistance (European Commission, 2016). Further, spreading bacterial resistance and a perpetuated decline in antibiotic effectiveness suggest that annual costs relating to resistance will increase as well. Through increased inspection, U.S. consumers will face less of a risk of antibiotic consumption and less of a threat of hosting resistant bacteria.

3. *International organizations and government authorities should advocate for veterinary style legislation in all exporting countries.*

There is little incentive for aquaculture producers to change their antibiotic use practices and risk protecting the health of their stock. Because aquaculture produced in dense CAFO's warrants the use of large quantities of antibiotics for health maintenance, a reduction in drug use will likely result in production loss or will force the producer to

change their production method. Evidence from the E.U., Norway, & Canada supports that requiring a veterinary assessment and prescription can reduce overall antibiotic use on a national level. Top-down governance has shown to be effective in reducing the overall use of medically important drugs in aquaculture. International organizations and food safety authorities can develop programs to assist and support foreign governments in designing regulatory and enforcement frameworks if they do not exist or are ineffective in a particular country. It is in the interest of both the E.U. and the U.S. to advocate for this restrictive regulatory style in countries they import from.

4. *More research should be focused towards alternatives to antibiotic use in aquaculture*. There have been gradual efforts to find new antibiotic alternatives that are less detrimental to human and environmental health. Antibiotic drugs are used in animal production to kill bacteria and reduce infection risk throughout production. Probiotics, bacteriophages and clays are some non-drug alternatives that have been used to perform the same tasks as antibiotics in aquaculture settings. So far these have only been used to control bacterial growth in experimental aquaculture operations and are not yet used commercially, specifically because the interaction and effectiveness of these bacteria and clays with different pathogenic bacteria are not fully understood (Jaejoon et al., 2016; Chuah et al., 2016). A coordinated global research effort towards finding alternatives would help to identify management practices that would allow for the transition away from antibiotic use in aquaculture.

These recommendations are only pieces to the antimicrobial resistance issue. Because this is a global threat, coordination between governments, private firms, non-profit organizations,

and academics are needed to holistically address antimicrobial resistance. The further progression of antibiotic resistance puts us all at risk of prolonged and potentially fatal infections, as antimicrobial drugs that have been used for decades grow increasingly less effective. The FDA's recent implementation of the Veterinary Feed Directive is a significant step in the direction of curbing antibiotic resistance in the U.S. Despite this new legislation, aquaculture imports may still undermine the FDA's efforts. Import rejection data and independent research has shown that antibiotics are undoubtedly being used in foreign aquaculture operations that export to the U.S. and that seafood imports are found to have antibiotic residues on them. Because such a small degree of U.S. seafood imports are inspected, it is highly likely that seafood harboring antibiotic residues and possibly resistant bacteria are accepted into the U.S. daily. Enhancements in U.S. inspection procedures and international agency involvement are vital steps the U.S. can engage in immediately. Additionally, encouraged advocacy for international restriction on antibiotic use and access, as well as strongly backed alternative drug research, support the goal for an international reduction in antibiotic use.

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Appendix

Table 1- Class, drug and description of all referenced drugs

Penicillin	Amoxicillin	Used to treat blood infections (septicemias), gonorrhea, meningitis, & endocarditis (inflamed heart valves)
Aminoglycosides	Streptomycin, Gentamycin, Neomycin	Used to treat digestive and respiratory diseases. As well as blood infections, and urinary diseases.
Nitrofurans	Furazolidone	Used to treat skin burns, urinary tract infections, cholera, & giardiasis.
Sulfonamides/ Sulfones	Sulfamonomethoxine, Sulphamethoxazole, Sulfadimethoxine, Sulfadiazine, Trimethoprim, Ormetoprim, Dapsone	Used to treat infections related to pneumonia, HIV, skin infections, & leprosy.
Quinolones	Enrofloxacin, Norfloxacin, Oxolinic Acid, Flumequine, Nalidixic Acid, Ciprofloxacin	Used to treat enteric and respiratory diseases. Also used as a treatment for blood infections and colibacillosis, a disease caused due to E. coli exposure.
Nitroimidazoles	Ipronidazole, Ronidazole, Metronidazole, Dimetridazole	Used to treat gastrointestinal, skin, and lower respiratory bacterial infections. Also used in the treatment of meningitis, diarrhea, and acne.
Amphenicol	Florfenicol, Thiamphenicol, Chloramphenicol	Used to treat bacterial infections connected to prostate glands and the eye. Also used as a treatment for pneumonia.