ABSTRACT

Biotechnology based products for animals may be regulated by one or more federal agencies. This prompted research into whether the acts, laws, regulations and guidance available were sufficient for an individual to write a successful request for jurisdiction to the United States Department of Agriculture – Center for Veterinary Biologics (USDA – CVB). A survey was conducted to collect information related to experiences and opinions of others. Survey results showed most study participants used resources available from the USDA – CVB website and consulted CVB, and believed the information available was not sufficient for a new regulator in industry to write a request for jurisdiction, indicating that additional written guidance from the CVB could be helpful to industry.

INDEX WORDS: Biotechnology, Animal, Jurisdiction, USDA, CVB, Guidance
JURISDICTION REQUESTS TO USDA-CVB FOR THE REGULATION OF BIOLOGICAL PRODUCTS FOR ANIMALS IN THE UNITED STATES

by

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JURISDICTION REQUESTS TO USDA-CVB FOR THE REGULATION OF BIOLOGICAL PRODUCTS FOR ANIMALS IN THE UNITED STATES

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CHAPTER 1
INTRODUCTION

Background

In the United States, biological products for administration to animals that are based on biotechnology may be regulated by one or more federal agency. As an example, a Manhattan Institute brief titled “The Liability and Regulatory Threat to Biotech” by Peter W. Huber described that a gene-altered vaccine for hogs may require review from five federal agencies in its development and commercial use. As Huber described, the National Institutes of Health oversees federally funded experimentation. The United States Department of Agriculture (USDA) regulates the commercial use of the vaccine. The Environmental Protection Agency (EPA) may become engaged through the Toxic Substances Control Act, and the Occupational Safety and Health Administration could oversee farm worker exposure. Finally, the Food and Drug Administration (FDA) could become involved for vaccine residues detected in bacon or other foods sourced from the vaccinated hogs.

Focusing on only the area of product registration for commercial use overseen by the USDA in the Huber example, biotechnology products can be plagued by a lack of clarity as to which federal agency will have oversight even in this one area. The USDA asserted jurisdiction over vaccines to reduce or eliminate bacterial colonization in animals even if the infection is rarely associated with significant clinical disease in those animals, while the FDA asserted jurisdiction if the same product had an implicit or explicit claim for food safety. The FDA assumed regulatory authority over contraceptives intended for use in domestic animals,
livestock, and wild animals held in captivity such as a zoo, while the EPA assumed regulatory authority over the same contraceptives intended for use in wildlife and feral animals, including wildlife that were opportunistically using zoo property. This seems to indicate in one case the jurisdiction can be based on the specific wording of the intended labeling claim during product registration, and in another case the jurisdiction could be dependent on the intention to use the product in captive or wild animals. These decisions can be confusing to a product developer or regulator attempting to navigate the appropriate product registration pathway with a new biotechnology product.

Area of Focus

Since the oversight of biotechnology products can be complex, the area of focus for this thesis was animal biological products, and more specifically on requests for jurisdiction to the USDA – Center for Veterinary Biologics (USDA-CVB) for these products. Animal biological products can be regulated either as biologicals under the Virus-Serum-Toxin Act (VSTA) or as drugs under the Federal Food, Drug, and Cosmetic Act (FDCA). The USDA broadly defines biological products for animals in Title 9 of the Code of Federal Regulations (CFR) Part 101.2 as all viruses, serums, toxins (excluding antibiotics) or analogous products, intended for use in the treatment of animals, and which act primarily through immune response. This includes but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components. The FDA broadly defines drugs for animals under FDCA (Section 201 [21 U.S.C. § 321] (g)(1)) as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in animals and articles (except food) intended to affect the structure or any function of the body of animals. In this way, animal biological products are also considered
drugs within the meaning of the FDCA, and FDA regulates animal biological products that do not conform to the VSTA.\textsuperscript{2} In essence, animal biological products that are not determined to be under CVB jurisdiction are likely to be under FDA jurisdiction, unless both regulatory agencies disclaim jurisdiction and another agency assumes oversight.

\textbf{Situation and Need}

In the 1980s Genentech reportedly encountered delays and expenses while the USDA – CVB and the FDA – Center for Veterinary Medicine (CVM) discussed for over a year which agency would regulate a bovine interferon product that was new at the time.\textsuperscript{29} As both agencies reportedly asserted jurisdiction, the company initially attempted to meet the requirements of both agencies.\textsuperscript{12} Ultimately the bovine interferon product became regulated by FDA,\textsuperscript{27} and an agreement was made between USDA and FDA in 1982 (Memorandum of Understanding (MOU) 225-82-7000) to reflect the responsibilities for regulating animal biological products as biologicals under the VSTA or as drugs under the FDCA.\textsuperscript{32} The substance of the agreement in this memorandum established a standing committee between the agencies to share information and decide jurisdiction, but the memorandum did not clarify through examples the types of cytokines and interferons regulated by FDA versus USDA until it was updated in 2013.\textsuperscript{2} The MOU of 2013 was an improvement by adding examples of the established or predicted product jurisdictions for each agency. Since it was a joint memorandum between the agencies, it lacked specific direction to industry as to how to successfully request a jurisdictional decision from the agencies.

While there are some similarities in the regulation of animal biological products by either USDA – CVB or FDA – CVM, there are also some significant differences in the licensing of new animal biological products under these agencies. Each agency developed its own set of
regulations and guidance documents to implement its regulations; therefore attempting to meet the requirements of both agencies as in the bovine interferon example can result in increased development costs and development project delays. If the jurisdiction of a product is not clear, then the developing company is responsible for consulting with the different regulatory agencies and confirming agreement on jurisdiction, in order for the company to most effectively navigate which regulatory pathway to follow while developing and licensing the product for commercialization.

Hypothesis

There are employees working for companies; and consultants or other personnel working with companies; that are responsible to review and give advice on the regulatory aspects of product development. This advice can be based on the legislative acts granting authority to a regulatory agency, the published laws and regulations, and guidance documents available from the agency, as well as their experience. If the jurisdiction of the product in development is unclear, then these individuals may prepare a jurisdiction request to the agency. The hypothesis of this research was the acts, laws, regulations and guidance available from USDA – CVB were insufficient to enable an individual to write a successful request for jurisdiction to USDA – CVB.

Desired Outcome

The purpose of this research was to determine if the information available in the public domain was sufficient for an individual to write a successful request for jurisdiction to USDA – CVB. Research included the review of historical and current regulations and guidance available from the USDA – CVB. This research also included the review of questions or issues faced by companies, and the review of articles available in the public domain describing jurisdiction under the VSTA. The hypothesis of this research was the acts, laws, regulations and guidance
available from USDA – CVB were insufficient to enable an individual to write a successful request for jurisdiction to USDA – CVB. A survey was conducted of individuals that own, work for, or may work with companies listed in the Veterinary Biological Products Licensees and Permittees book available on the USDA website. This book lists all companies that hold at least one biological product license issued by USDA. By selecting individuals from these companies, and by selecting consultants or other persons that may work with these companies, it was surmised that individuals with experience or knowledge in regulations administered by USDA – CVB could be contacted. Among these personnel, some individuals that review and give advice on the development of animal biological products would have experience in making jurisdiction requests to USDA – CVB. Results of the survey were desired to collect these experiences and accept or reject the research hypothesis.
CHAPTER 2
HISTORY OF THE AGENCIES AND MODERN REGULATIONS

USDA, FDA, and Legislative Acts

The United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) were linked historically. President Abraham Lincoln signed a bill in 1862 to establish the USDA, and the first Commissioner of Agriculture established the Chemical Division. The Chemical Division became the Division of Chemistry in 1890 and the Bureau of Chemistry in 1901. The USDA was tasked to regulate drugs after President Theodore Roosevelt signed the Federal Food and Drugs Act in 1906 and entrusted implementation of the law to the Bureau of Chemistry of the USDA. Drugs included medicines, preparations, substances, and mixtures of substances intended to be used to cure, mitigate, or prevent disease of man or animals. The 1906 law rendered it unlawful for any person to manufacture within the United States any drug which was adulterated or misbranded and prohibited the introduction into any state from any other state drugs which were adulterated or misbranded. In summary, in 1906, the USDA regulated drugs for both man or animals.

The Viruses, Serums, Toxins, Antitoxins, and Analogous Products Act, also known as the Virus-Serum-Toxin Act (VSTA), was enacted in 1913. The VSTA was the result of the hog industry suffering substantial losses from the unregulated manufacture and distribution of anti-hog cholera serum, after which a USDA official testified that a bill was necessary to protect United States farmers and livestock raisers. The 1913 law rendered it unlawful for any person, firm or corporation to prepare, sell, barter, or exchange in the United States; or to ship or deliver
for shipment from one state to another; a worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals.49

The 1913 VSTA was strengthened by including provision that the products for animals be prepared at a licensed establishment in compliance with regulations prescribed by the Secretary of Agriculture.49 This was similar to the Biologics Act of 1902, enacted following the distribution of a diphtheria antitoxin contaminated with tetanus24,40 and a contaminated smallpox vaccine that resulted in the death of several children.40 While the Biologics Act of 1902 administered by the Public Health Service was strengthened by establishing licenses and allowing government inspections to certify the human biologics were prepared properly before sale, and the 1913 VSTA administered by the USDA followed suit for animal biologics, the 1906 Federal Food and Drugs Act did not provide for pre-market approval and was weakened by political pressure and court challenges during that time period.40 A 1917 report of the USDA Bureau of Chemistry described the Food and Drugs Act contributed to safeguarding people’s health, but lacked restrictions on the use of many of the most virulent poisons in drugs and failed to address fraudulent advertising for drugs made outside of the drug packaging.24 To summarize the regulatory landscape in 1917, the USDA regulated human and animal drugs under the 1906 Federal Food and Drugs Act, and animal biologics more strongly under the 1913 VSTA, while the Public Health Service regulated human biologics.

The USDA Bureau of Chemistry became the Food, Drug, and Insecticide Administration in 1927 and became the Food and Drug Administration (FDA) in 1930.24 A 1933 report of the FDA encouraged the overhaul of the 1906 Federal Food and Drugs Act.24 Walter Campbell, the chief of the FDA, and Rexford Tugwell, the Assistant Secretary of Agriculture, began the process,7,43 which led to a bill that was ultimately introduced by the Senate sponsor Royal
The revised bill preserved the 1906 law and added, among other things, the prohibition of false advertising and provided for more effective methods to control false labeling and advertising of drugs, classified a drug as adulterated if it could be dangerous to health under the conditions of use prescribed in its labeling, and prescribed the operation of factories under Federal permit where public health protection could not otherwise be effected. There was a provision requiring safety testing before marketing new drug products that had been removed from the bill, but it was restored in response to the deaths of over 90 people including children from Elixir Sulfanilamide containing diethylene glycol as a solvent, and the Federal Food, Drug and Cosmetic Act (FD&C Act) was signed by President Franklin D. Roosevelt in 1938. In defining adulterated and misbranded in the FD&C Act, and describing circumstances in which a drug was adulterated or misbranded under the law, the 1938 Act changed the scope of the FDA’s responsibilities. With the 1938 Act, the path for the USDA and FDA as federal agencies began to diverge. The FDA was transferred from the USDA to the Federal Security Agency in 1940, before being transferred to the Department of Health, Education, and Welfare in 1953, which became the Department of Health and Human Services in 1979. In brief, the FDA was given a new scope with stronger authority under the FD&C Act in the 1930s and then separated from the USDA.

While the VSTA of 1913 remained unchanged for decades, the FD&C Act was amended many times since 1906. There was no distinction between drugs for humans and animals; therefore most of the requirements of the 1906 and 1938 FD&C Acts applied to animal drugs. The Drug Amendments of 1962 were notable in the history of drug regulation by requiring premarket approval of the safety and effectiveness of new drugs, placing the burden of proof on companies, and drugs that were currently on the market were subject to review by the National
Academy of Sciences under the drug efficacy study implementation program. These requirements applied to new animal drugs until the Animal Drug Amendments of 1968, which retained some of the broad concepts such as the criteria and procedures for new animal drug approvals but introduced some distinctions reflecting differences in how animal drugs were manufactured, distributed, and administered. In this way, some separation between human and animal drugs began to take hold in the regulations administered by FDA after 1968.

Jurisdiction over products also changed over this time. The responsibility for the Biologics Act was transferred from the Public Health Service to the FDA in 1972, thus FDA had authority over human and animal drugs, and human biologics, while USDA had authority over animal biologics. This is in contrast to the regulatory landscape only 55 years earlier, in 1917, when the USDA regulated human and animal drugs under the 1906 Federal Food and Drugs Act, and animal biologics under the 1913 VSTA, while the Public Health Service regulated human biologics.

The distinction in 1972 in which FDA had authority over human and animal drugs and human biologics; and USDA had jurisdiction over animal biologics; may seem clear. In practice, as seen in lawsuits filed in 1978 against the USDA and in 1979 against the FDA, there remained confusion. In 1978, the Animal Health Institute and Colorado Serum Company filed a complaint against the United States Department of Agriculture, contending the USDA was not enforcing the VSTA against unlicensed veterinary biological drug manufacturers. USDA interpreted they did not have the authority to regulate producers that operated within a state. The Virus-Serum-Toxin Act only authorized regulation when shipment crossed state lines. The United States District Court of Colorado agreed with USDA in their 1980 decision, citing in the brief that the legislative history of the Virus-Serum-Toxin Act was extremely sparse but supported the view
that Congress did not intend to require licensing of intrastate manufacturers.\textsuperscript{1} The Biologics Act of 1902 excluded producers that operated within state boundaries, and the Virus-Serum-Toxin Act of 1913 for animal biologics was modeled after the 1902 Act for human biologics. The district court decided that Congress would have to pass legislation if Congress wanted the USDA to oversee manufacturers of animal biologics that confined their activities to one state.\textsuperscript{1}

In 1979, two FDA field officers attempted to inspect Grand Laboratories, Inc. facilities where animal biologics were manufactured and distributed wholly within the state of South Dakota.\textsuperscript{22} In Grand Laboratories, Inc. v. Harris, the company brought suit against the FDA on the grounds that FDA did not have jurisdiction to regulate the manufacture and sale of animal biologics.\textsuperscript{22} With the Animal Health Institute v. USDA decision in 1980, the USDA also did not have jurisdiction over Grand Laboratories, Inc., because Grand Laboratories was operating wholly within one state, even though a component used in the biologic may have passed through interstate commerce.\textsuperscript{22}

The FDA asserted jurisdiction over animal biologics for intrastate manufacturers by defining these products as drugs under the FD&C Act.\textsuperscript{22} The United States District Court of South Dakota disagreed with the FDA because the term “drug” was defined in the Act of 1906, the definition had not materially changed since then, and the definition of “drug” did not encompass animal biologics as evidenced by Congress passing the Virus-Serum-Toxin Act in 1913 rather than amending the 1906 Act.\textsuperscript{22} The FDA appealed that animal biologics were “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” meeting the literal definition of section 321(g)(1)(B) of title 21 to allow FDA jurisdiction.\textsuperscript{22} In the analysis by the court of appeals, the FD&C Act of 1938 did not reference animal biologics, but section 902(c) was amended with the Animal Drug Amendments
of 1968 to specifically exempt the 1913 Virus-Serum-Toxin Act from jurisdiction of the FD&C Act,\textsuperscript{22} supporting that products that would be regulated by USDA under the VSTA when crossing state lines would not fall to FDA jurisdiction when operating wholly within one state. Furthermore, it was noted that FDA’s regulation in title 21 of the Code of Federal Regulations section 7.1(f) in 1980 defined products under FDA jurisdiction included “any food, drug, and device intended for human or animal use, any cosmetic and biologic intended for human use”.\textsuperscript{22} The majority decision of the court was if the scope was meant to include animal biologics, then the sentence could have been “any food, drug, biologic, and device intended for human or animal use” and could have differentiated only cosmetics as intended for human use. Therefore, the United States Court of Appeals, Eighth Circuit ruled in favor of Grand Laboratories, Inc. (Heaney, Gibson; dissent by Arnold) and decided in 1981, similar to the Animal Health Institute v. USDA case, that the gap left for intrastate manufacturers was up to Congress to close rather than the judicial branch.\textsuperscript{22}

The decision in Grand Laboratories, Inc. v. Harris made by the United States Court of Appeals, Eighth Circuit was reversed in 1981, with two judges dissenting, after granting the FDA’s petition for rehearing\textsuperscript{22} before the entire bench of judges rather than by a panel of judges. In this decision, the United States Court of Appeals for the Eighth Circuit (en banc) explained that it was their duty to attempt to harmonize the Federal Food and Drugs Act of 1906 and the Virus-Serum-Toxin Act of 1913 by giving effect to both of them to the extent possible, and that the definition of a drug from 1906 as “any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals” was valid and did give FDA jurisdiction over intrastate commerce of animal biologics.\textsuperscript{22}
As a result of these cases, the Virus-Serum-Toxin Act of 1913 was amended by Congress in the Food Security Act of 1985 to make intrastate and exported animal biologics subject to the Virus-Serum-Toxin Act, to strengthen USDA authority to issue regulations, and to enhance USDA enforcement abilities. A Senate report referred to these two court cases and jurisdictional issues between USDA and FDA as reasons to update the law and preserve USDA authorities.

With no further amendments to the Virus-Serum-Toxin Act since 1985, the USDA currently has jurisdiction over VSTA regulations and policies. USDA jurisdiction includes exports, with some exceptions afforded by the FDA Export Reform and Enhancement Act of 1996. USDA jurisdiction also includes imports, with coordination of regulatory and inspection practices with the Department of Homeland Security since the movement of certain activities such as border inspection functions under the Homeland Security Act of 2002. Overall, with one amendment to the 1913 VSTA that occurred in 1985, and no amendments to the act in 1986 through 2018, there has been a relative stability in the VSTA for governing animal biologics.

For FDA, amendments relevant to animal drugs since 1985 included the Generic Animal Drug and Patent Term Restoration Act of 1988, and the Drug Export Amendments of 1986 provisions which were replaced with more lenient provisions in the FDA Export Reform and Enhancement Act of 1996. Congress enacted the Food and Drug Administration Modernization Act in 1997 to reform FDA regulation, granted user fee authority for animal drugs in 2003, and in 2004 amended animal drug provisions of the FD&C Act relating to prescription animal drugs, the new animal drug approval process, and animal drugs for minor species. This showed that Acts governing animal drugs continued to change and were refined since 1985 to present.
Regulations, Guidance, and Other Literature

Reviewing literature for the origin and historical language surrounding the Acts was helpful, as was reviewing the regulations written by the USDA in Title 9 of the Code of Federal Regulations (CFR) compared to those written by the FDA in 21 CFR. In addition to the regulations from the agencies being separate, the guidance documents written by USDA and FDA to elaborate on their thinking was also very separate and was hosted on different websites by each agency.5,23 There exists an FDA guidance document “How to Write a Request for Designation (RFD)”,25 that could be used to successfully write a request to the FDA to determine which FDA Agency Center will regulate a product. This guidance for RFD could in theory be used as a model to write a request for jurisdiction to FDA or USDA. However, there was no guidance for industry identified on the USDA – CVB or FDA – CVM websites to truly direct personnel on how to write a request for jurisdiction to the USDA and FDA for a new biological product for animals.

The regulations, guidance documents, and other documents describing matters of jurisdiction between USDA and FDA are summarized, beginning with the jurisdictional questions discussed in the 1980 and 1981 court decisions Animal Health Institute v. the United States and Grand Laboratories, Inc. v. Harris. These two court cases contributed to document number MOU 225-82-7000 “Memorandum of Understanding Between The Animal and Plant Health Inspection Service United States Department of Agriculture and The Food and Drug Administration Department of Health and Human Services” issued in 1982. This Memorandum of Understanding (MOU) reflected USDA and FDA’s understanding of their responsibilities for regulating animal biological products as biologicals under the VSTA or as drugs under the FDCA.32 The memorandum described USDA and FDA agreed to provide to each other any
information coming to their attention regarding veterinary products that could be relevant to the 
other agency’s enforcement functions under VSTA or FDCA.

The advancement of biotechnology, including the need for the agencies to determine the 
jurisdiction of bovine interferon also contributed to the MOU in 1982. As both agencies 
asserted jurisdiction, and attempts to resolve the impasse using scientific grounds failed initially, 
the company incurred additional costs and burden by attempting to meet the requirements of both 
agencies. Eventually Genentech’s bovine interferon product became regulated by FDA. The 
1982 memorandum admitted there was a new generation of biological products to treat diseases 
in animals, and aspects of these products could be significantly different from the past. As a 
result, the way that USDA and FDA traditionally decided who would have jurisdiction might not 
apply to these products. A standing committee with members from each agency was established 
to meet and consider the regulatory responsibility over these new products. This MOU was an 
improvement by establishing a forum for the agencies to discuss jurisdictional questions, but it 
did not give companies or researchers direction for how to request a decision of jurisdiction from 
the agencies.

The advancement of biotechnology gave the U.S. Congress Office of Technology 
Assessment (OTA) a reason to evaluate the federal regulations in the 1980s, both internationally 
and nationally, and in January 1984, the OTA issued its report analyzing the competitive position 
of the United States in regards to the commercial development of new biotechnology. USDA – 
CVB meanwhile issued a guidance document in December 1984, titled “New Biotechnology for 
Preparation of Animal Biological Products” (Veterinary Services Memorandum (VSM) No. 
800.68), to establish that new biotechnological procedures such as recombinant DNA, chemical 
synthesis, or hybridoma technology would be treated as analogous to products prepared by
conventional techniques. In summary, it was determined that new biotechnology could be regulated under existing rules.

Shortly thereafter, the Virus-Serum-Toxin Act of 1913 was amended by the Food Security Act of 1985. This was critical to overturn the decision made by United States Court of Appeals, Eighth Circuit, which had granted authority to the FDA to regulate biological products for animals when wholly within one state. The court cases contributed to amending the VSTA, and Congress asserted USDA would have authority for intrastate jurisdiction of biological products for animals.

In June 1986, a study report by the White House Office of Science and Technology Policy (OSTP) entitled the “Coordinated Framework for the Regulation of Biotechnology” was issued for public comment. The OSTP report summarized relevant federal laws and policies and concluded no new legislation was needed. The report described jurisdiction was determined by the use of the product, as had been the case traditionally. It urged agencies to adopt scientifically consistent standards, and suggested a single agency exercise responsibility over a given product whenever possible, with designation of a lead agency where two or more agencies overlapped in responsibilities. Taken together, the OTA report, CVB guidance VSM No. 800.68, and the OSTP report indicated that the law in effect in the mid-1980s was deemed sufficient to handle biotechnological advancements, and if there were questions regarding which federal agency had jurisdiction, then the federal agency could be contacted.

Although the federal government was aligned that existing rules were sufficient, the National Agricultural Law Center of the University of Arkansas published a research article in the Drake Law Review in 1989 that disagreed with this stance. The article summarized FDA and USDA regulations since 1986 and acknowledged the position maintained by the agencies that
existing frameworks with no new regulations or administrative procedures were necessary to
deal with general concerns about biotechnology. The article then described evidence that the
regulations did require some clarification. One example described a 1986 policy statement by
FDA to require only a supplemental application for a biotechnology product virtually identical to
an approved, conventional technology, animal drug. The policy statement was in contrast to
other documents from the FDA taking the position that new drug applications would be
necessary for all recombinant DNA products. Similarly, USDA’s guidance document VSM No.
800.68 identified a new product using recombinant DNA technology was treated as analogous to
conventional products, yet also referenced National Institutes of Health guidelines that did not
apply to conventional products. The 1989 article in the Drake Law Review touched on this
confusion when it described the USDA awarded a license to produce and sell a genetically
engineered vaccine to combat pseudorabies virus in 1986, and after the vaccine was reclassified
as recombinant it raised the question of whether National Institutes of Health guidelines would
apply. The vaccine product license was temporarily suspended while the USDA prepared a
formal environmental assessment and justified lifting the license suspension.

Thus, as the 1980s came to a close, a company that needed clarity regarding the
jurisdiction of its product could consult the Memorandum of Understanding between USDA and
FDA from 1982 and the Coordinated Framework of 1986, could glean some details regarding
new biotechnology policies from USDA from VSM No. 800.68, and could consult the USDA to
discuss a new product believed to be an animal biologic subject to the VSTA. Unfortunately,
none of these documents conveyed the specific process to submit a request for jurisdiction to
USDA – CVB or described the type of information that should be included in a request.
In reviewing literature for developments regarding USDA jurisdiction in the 1990s, it was noted the Coordinated Framework for biotechnology was updated in 1992. More importantly, in 1998 the definition of animal “biological products” was revised. 9 CFR 101 in 1997 defined biological products as “…all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals.” In 1998, the 9 CFR 101 was revised to state “…all viruses, serums, toxins (excluding substances that are selectively toxic to microorganisms, e.g. antibiotics), or analogous products at any stage of production, shipment, distribution, or sale, which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The term “biological products” includes but is not limited to vaccines, bacterins, allergens, antibodies, antitoxins, toxoids, immunostimulants, certain cytokines, antigenic or immunizing components of live organisms, and diagnostic components, that are of natural or synthetic origin, or that are derived from synthesizing or altering various substances or components of substances such as microorganisms, genes or genetic sequences, carbohydrates, proteins, antigens, allergens, or antibodies…” The definition in 1998 went on to describe the need for an objective standard to determine the product’s intended use based on factors such as representations, claims, packaging, labeling or appearance. It further elaborated on what the term analogous products included, and defined treatment as “…the prevention, diagnosis, management, or cure of diseases of animals.”

Revising the definition of a biological product for animals in the regulations in 1998 provided some clarification for USDA jurisdiction. For example, antibiotics were clearly
excluded while certain cytokines of synthetic origin were included, a primarily immunological mode of action was required, and the nature of product’s intended use came into the assessment. Examples of what certain cytokines were regulated by USDA as opposed to FDA was found in an update to the Memorandum of Understanding in year 2013, but first there were a number of documents issued or published in the 2000s as summarized below.

In 2003, the USDA issued Veterinary Services Memorandum (VSM) 800.205 to provide guidance for the submission of risk-related documents when pursuing licensure of biotechnology-derived veterinary biological products. This memorandum did not discuss jurisdiction concerns, but it categorized and gave some examples of biological products such as monoclonal antibodies for therapeutic or prophylactic use and monoclonal antibodies and expressed proteins for use in diagnostic test kits. Based on the examples canine lymphoma monoclonal antibody, and plasmid-expressed equine infectious anemia virus p26 and gp45 proteins in a diagnostic kit, it could be assumed that similar examples of biological products would be regulated by USDA.

To provide clarity for the jurisdiction of products targeted against carrier state organisms, in 2005 the USDA issued a notice explaining the USDA and FDA agreed that animal vaccines targeted to reduce or eliminate a carrier state of organisms that could infect other animals would lie with USDA – CVB, provided certain criteria were met. The notice explained that the criteria to determine CVB jurisdiction for carrier state organisms included an intention to administer the product to animals, a primary action through immune system modulation or response, and the product could not include food safety and human health labeling claims. The notice was further explained in a United States Animal Health Association document in 2005 regarding *E. coli* as an example. Similar to the regulation change in 1998 to clarify the definition of a biological
product, this guidance document reiterated an immunological mode of action was required and the nature of a product’s intended use was considered when determining whether USDA or FDA would have authority over a product.

Also in the mid-2000s, specifically in 2006, the USDA Wildlife Services - National Wildlife Research Center reported on jurisdiction confusion for wildlife contraceptives.\textsuperscript{17} After a decade of FDA overseeing such products, the jurisdiction was questioned, because wildlife contraceptives were deemed incompatible with the FDA – Center for Veterinary Medicine (FDA – CVM) regulatory process, and outside the regulatory authority of USDA – CVB.\textsuperscript{17} Ultimately the U.S. Environmental Protection Agency assumed authority of contraceptives for wildlife and feral animals, while FDA – CVM retained authority for uses in captive animals including livestock, companion animals and zoo animals.\textsuperscript{17} Taking from the definition of a biological product in the regulations, the product was outside the authority of CVB since the prevention of pregnancy is not the prevention, management or cure of an animal disease.

As previously alluded to, the Memorandum of Understanding between USDA and FDA was revised and approved in 2013.\textsuperscript{2} This revision was helpful by providing an updated list of products established to be regulated by FDA or by USDA, and included by example some clarification as to which certain cytokines were regulated by USDA. Unfortunately, as a memorandum between the agencies, it still did not give specific, detailed guidance to companies for how to submit a request for jurisdiction to the USDA – CVB. The MOU implied a company should authorize the release of information between the agencies, and identified the liaison officers of each agency to submit information to concerning products that pose jurisdictional questions. The MOU was also made available and accessible from the USDA – CVB Policy, Evaluation and Licensing Manual, part 3.5.\textsuperscript{15}
A few years later, in 2016, the USDA – Wildlife Services published “A Decision Support Tool for Determining Federal Regulatory Authority over Products for Vertebrate Animals”. The article described determining the regulatory jurisdiction could be confusing for product developers, and provided a decision tree to help researchers identify the regulatory jurisdiction. The article described a product was classified by the intended use, mechanism of action, potential or known hazards, and characteristics of the vertebrate animals or disease organisms on or against which the product would be used. The article stated clearly that the decision trees were not endorsed or approved by the federal regulatory agencies that it described, and due to regulatory guidance being subject to change over time, it suggested that researchers consult the agencies early to verify jurisdiction and ensure compliance. Although not endorsed by the agencies, the article helped describe one pathway to USDA – CVB jurisdiction was for a product that appeared reasonable and consistent with CVB Notice No. 05-07 as:

- Was intended to target microorganisms, or targeted against internal parasites, or both internal and external parasites of vertebrate animals, that cause parasitic disease
- Was applied in or on living animals, or in animal feed or drinking water
- Had a primary mechanism of action or diagnostic results from a direct immunological function in the animal
- Carried no human health or food safety claims.

Another pathway described in the publication was for a product to diagnose, treat, or prevent a symptom of a non-infectious disease in a vertebrate animal. The primary mechanism of action or diagnostic was again a direct immunological function in the animal, and no human health or food safety claims could be made. This pathway showed that if it was unclear if the mechanism of action was “direct”, then the joint FDA and USDA jurisdictional committee would
determine which agency had authority. This demonstrated the importance of the mode of action, which was up to the developer to determine and to describe to the agencies.

Another update to the Coordinated Framework for the Regulation of Biotechnology was released in 2017. It was accompanied by a document titled the National Strategy for Modernizing the Regulatory System for Biotechnology Products. The update was found to be available from the USDA – Biotechnology and Regulatory Services (BRS) – Meetings web site,30 which is the section of the agency that implements regulations for certain genetically engineered organisms that may pose a risk to plant health.6 The Coordinated Framework update was not found linked to the animal biologics guidance from USDA – CVB;5 therefore it did not appear that this document was recommended by CVB to industry as a resource to determine product jurisdiction. Nevertheless, the framework was helpful by acknowledging that today it can still be challenging for businesses to navigate the regulatory process for biotechnology products,31 and it reconfirmed the decision that a veterinary biological product for animals was under the purview of FDA – CVM if it was not in full conformance to the VSTA to make it subject to USDA – CVB. Unfortunately, the hypothetical case studies in the framework document did not include a potential veterinary biological product, and focused mainly on hypothetical plants and plant products. The accompanying document for the National Strategy for Modernizing the Regulatory System for Biotechnology Products described the FDA and USDA were committed to interagency communication to help with timely regulatory jurisdiction decisions, in order to help clarify for developers which agency or agencies might have oversight,33 but the strategy document neither defined a time limit for a jurisdiction decision nor gave direction to developers as to how to submit a request for jurisdiction to help support the agencies in making a timely decision.
Summary of Literature

In summary, Genentech experienced delays and additional costs in product development when the jurisdiction of their product was under debate, and the legal cases Animal Health Institute v. the United States, and Grand Laboratories, Inc. v. Harris indicated that the jurisdiction of biological products were unclear in the 1980s. Contrary to the majority decision made en banc by the United States Court of Appeals, Eighth Circuit, the Virus-Serum-Toxin Act was amended by Congress in 1985 to grant jurisdiction to the USDA for biological products that were intrastate or exported. While there was no need for new legislation over biotechnology products as described in the “Coordinated Framework for the Regulation of Biotechnology” report first issued in 1986, a publication in the Drake Law Review in 1989 described evidence that the regulations required some clarification. These examples show that in the 1980s the jurisdiction of biological products for animals was not always clear.

Revising the definition of a biological product for animals in the regulations in 1998 provided some clarity for USDA jurisdiction, and CVB issued Veterinary Services Memorandum No. 800.205 in year 2003 for submitting risk-related documents when pursuing a license for a biotechnology-derived biological product. This was followed by a few other examples discussing specific types of products and clarifying the jurisdiction for those products. However, in general, the jurisdiction of a new biotechnology product could still be unclear. In 2016 a publication from the USDA – Wildlife Services described that it could be confusing for product developers to determine the regulatory jurisdiction of their product, and in 2017 when the Coordinated Framework was updated, it was acknowledged that it can still be challenging for businesses to navigate the regulatory process for biotechnology products. These statements that it could be confusing or challenging for businesses was anecdotally supported by a
description at the June 15, 2017 Animal Health Institute meeting in Ames, Iowa that USDA – CVB personnel met with FDA over a two day period, made headway on their definition of a biologic, and cleared nine pending jurisdictional issues. Similarly, in the September 19 - 20, 2017 Association of Veterinary Biologics Companies meeting in Ames, Iowa, it was described that monoclonal antibodies were debated by USDA and FDA. It was clarified that antibodies were under USDA – CVB jurisdiction unless there was a compelling reason otherwise, such as targeting against a specific drug, thus deciding the jurisdiction of ten items that were under discussion by the agencies.

While conducting a literature review on the subject of jurisdiction, one of the questions developed was which biological products for animals were overseen by USDA – CVB and FDA – CVM. The Memorandum of Understanding (MOU) between APHIS and the FDA approved in 2013 was an improvement in that it was more clear than its 1982 counterpart by providing a list of established jurisdictions that one could compare their product to, and by specifying the products regulated under the VSTA are intended for use to diagnose, cure, mitigate, treat, or prevent disease in animals and work primarily through an immune process. However, the MOU did not elaborate on what types of data, if any, were required to demonstrate the primary mode of action. As the literature review continued during this research, the initial question for which products were overseen by each agency developed into questions regarding how to submit a jurisdiction request to the agencies. While the MOU of 2013 was useful in that it provided examples of products overseen by each agency, it was decided that as biotechnology continues to evolve, a comprehensive list of all products would be impossible to create and maintain.

The research question of how to submit a jurisdiction request to the agencies was refined in scope to focus on the USDA – CVB. The guidance available from the USDA – CVB in
general is very helpful and instructive by explaining what to include in a submission. For example, Veterinary Services Memorandum 800.20045 describes in great detail the content to include in a study protocol and a final report. In addition to guidance documents, the CVB shares information such as their Policy, Evaluation, and Licensing Reviewer (CVB – PEL) Manual through their Biologics Regulations and Guidance web site. CVB – PEL Manual part 4.5.1, for example, describes in specific detail what to include in a request for an exemption to animal safety testing, and the items that must be addressed in an updated production outline. Unfortunately, there was no direct guidance located from CVB web site conveying the information needed to prepare a request for jurisdiction to USDA – CVB.

Specific to jurisdiction requests, the MOU described the agency that brought forth an issue for resolution was responsible for notifying the applicant and securing authorization to share confidential business information, whereas a guidance document written by CVB to industry could direct an applicant proactively to include such a statement in their request. The MOU described that such information would be provided to the liaison officers of the agencies, but a guidance document by CVB to industry could clarify if an applicant should submit requests for jurisdiction to these liaison officers or whether they should work the CVB – Policy, Evaluation and Licensing reviewer normally assigned to their company.

In conclusion, the CVB provided a clear and comprehensive Biologics Regulations and Guidance web site that provided useful and direct guidance to business to develop and license biological products under their jurisdiction. However, the CVB did not provide a guidance document to direct industry on how to write and submit a successful request for jurisdiction if the authority to oversee a new product was unclear. Since it is important to understand which agency has jurisdiction over a biological product in order for a product developer to ensure
compliance with the correct regulations during the development process, it could be helpful to industry to have a guidance document describing the details that should be included in a request for jurisdiction submitted to CVB.
CHAPTER 3

METHODOLOGY

Hypothesis

Based on review of the literature, my interpretation was the acts, laws, regulations and
guidance available from USDA – CVB were insufficient to enable an individual to write a
successful request for jurisdiction to USDA – CVB. Since regulatory interpretations can vary
based on an individual’s knowledge and experiences, it was determined that capturing data from
other professionals in industry was needed to evaluate the hypothesis.

Sample Population

The desired population of study participants was professionals with knowledge and
experience in submitting a jurisdiction request to CVB. These personnel could have been
employed by a company that was regulated by the USDA – CVB, either in the present or the
past. They could have been in research and development, regulatory affairs, quality, or other
roles. They could have been private practice veterinarians, or consultants who provided services
to companies that were regulated by the CVB. It was decided that the starting point to locate
study participants was to consult companies that held at least one license for a biological product
regulated by the CVB at the time that the possible study population was being estimated.

The USDA maintains a product code book made available electronically that is published
quarterly. It lists the companies that produce or import biological products regulated by the
USDA – CVB. As described in Chapter 2, the definition of a biological product according to
Title 9 of the Code of Federal Regulations is broad. This list of companies includes
manufacturers of vaccines, bacterins and bacterial extracts, bacterin-toxoids, toxoids, vaccines with bacterins or bacterial extracts or toxoids, antibody products, antitoxins, diagnostic products, and miscellaneous products including allergenic extracts, immunotherapeutics, immunomodulators, immunostimulants and vaccines against specific canine cancers. The list also includes companies that hold a product license to perform a major manufacturing step for these products, where more than one company is involved in the joint manufacture of a product.

In preliminary research, according to the USDA Veterinary Biological Products Licenses and Permittees list dated January 4, 2017, it was determined there were approximately 89 biologics companies regulated by USDA – CVB. At that time, USDA – CVB reportedly received on average one jurisdiction request per month. This was a relatively small population from which to collect study participants, and the calculation of sample size was complicated by the fact that approximately 12 jurisdiction requests within a year could have been accrued from between 1 and 12 requestors. This meant not all companies would have employees with experience in jurisdiction requests directed to USDA - CVB. Conversely, a single company could accumulate multiple employees with this type of experience. In summary, approximately 89 companies regulated by USDA – CVB did not necessarily mean that the population of individuals that must create a request for jurisdiction was sized at 89. Nevertheless, without more precise values for estimation, using a population size of 89, confidence level 95%, at margin of error 20%, the calculated sample size was 20.

In order to achieve this sample size among the small population of biologics companies regulated by USDA – CVB, the sample population included not only employees of these companies but also employees of animal health organizations and consultants to these companies. These organizations and consultants could have direct experience in creating a
request for jurisdiction to CVB, or they could have contacts with experienced personnel such that the survey could be forwarded to others with knowledge to share.

The USDA Veterinary Biological Products Licenses and Permittees list contained company names and postal mail addresses, but did not include any employee names, phone numbers or email contact information. A singular database containing contact information for biologics companies was not found in the public domain or on the USDA website, and email addresses for potential study participants could not be obtained from USDA – CVB through a Freedom of Information Act request due to considerations of privacy. As a result, the list of regulated companies available from the Veterinary Biological Products code book was used to identify potential companies, and then contact information was mined from the individual biologics company websites, professional networking sites such as LinkedIn, professional member organization contact lists, and finally was supplemented with private contacts.

Survey Development

One of the initial questions during preliminary research was how to determine if a product under development would be under the jurisdiction of CVB. Research into that question led to the question of how to make a request to CVB to request a determination of jurisdiction. This led to the hypothesis that the acts, laws, regulations and guidance available from USDA – CVB were insufficient to enable an individual to write a successful request for jurisdiction to USDA – CVB. This became the hypothesis to be tested.

Early in the survey development process, two options were considered: a written survey or a verbal interview to collect data. The primary reason that a verbal interview was undesirable was the need for openness. While the hypothesis that further clarity from the USDA – CVB was necessary was not in any way a criticism of the agency, it could have been misinterpreted as
such. It was decided that openness from respondents could be better achieved by providing a written survey that allowed the respondent to consider and craft whether they chose to share additional comments that could provide further insight into their experiences. The second reason that a verbal interview was deemed undesirable was the time required to complete the survey, since the process of an interviewer verbally reading the options would have taken longer than allowing a participant to visually read the options themselves. Lastly, during the earlier stages of survey development, it was thought that some respondents would need to recall experiences from years earlier and possibly review records to answer some questions. A written survey that could be set aside temporarily and completed later could improve the chances of receiving these answers, whereas during a verbal interview the study participant could have chosen easily to skip answering.

The types of questions to ask evolved during the development of the survey. Some open-ended questions written initially were transformed into multiple choice questions as the possible answers were developed. Frequently these multiple choice questions retained an open ended component, for example a question would include an option to identify an answer not listed as an option.

Multiple choice questions consisting of three or more options were most commonly designed into the survey, with some questions asking for a single answer and some questions asking for several or all applicable answers. This type of question was selected to allow for study participants to complete the survey quickly; and also to help standardize the data to allow for the straightforward analysis of results. As the multiple choice questions were designed, the use of checkboxes and drop down lists were designed into the survey.
The dichotomous question format was used to ask respondents with experience making at least one jurisdiction request if they believed the resources available were sufficient for a new regulator to make a jurisdiction request, in order to capture a clear opinion from the survey participants. Conversely, only for very experienced survey participants, a rank-order scale question was included to ask survey participants to identify the importance of written and human resources used to develop a request for jurisdiction. This question was designed to be answered by only the very experienced participants since it forced the discrimination of the choices among its alternatives, whereas the same question would not be applicable to an individual with no formal experience.

As survey questions were developed, efforts were made during revision of the survey to write short questions (meaning one to two lines) that were direct. It was necessary in some cases to include explanatory notes to help define the scope of a question, or to give specific direction to try to avoid the collection of sensitive information such as the names of individuals. In these cases, attempts were made to format instructions so they were separated from the questions by an empty space.

The length of the survey combined with the targeted demographic was found to be the most difficult aspects to develop into the survey. First of all, knowing that the calculated sample size was 20, among the small estimated population of only 89 biologics companies regulated by CVB, it could be challenging to achieve the desired sample size. Secondly, the survey participants could have a varied background and experience. During survey development it was discussed that individuals with some experience making a jurisdiction request could have a different opinion than individuals with a lot of experience. In addition, there could be individuals with no formal experience yet, that nevertheless had developed an opinion. This
variety of experience made it difficult to ask singular questions that were clear and direct. For example, a question posed to an individual with no experience would be asked what they would do (prospective). A similar question posed to an individual with some experience would be asked what they did (retrospective). A similar question posed to an individual with multiple experiences would be asked the retrospective question, with the addition of clarifiers as to whether an answer from their first experience or from their most recent experience was being sought. This became problematic very early in the development of the survey, and it was decided that the survey would be split into sections based on the level of experience. This design choice combined with the earlier decision to utilize largely multiple choice questions made the survey appear very lengthy at 12 pages, and it required the addition of directional questions to help guide the survey participants to complete only the section(s) applicable to them based on their experience. However, the use of multiple choice questions also made it possible to complete the survey quickly, in approximately ten to 20 minutes.

Another aspect discussed was how chronological time could have an impact on survey responses. Since regulations and guidance changed over time as described in chapter 2, a respondent making a jurisdiction request in 1980 may have had a very different encounter compared to a respondent making a request in year 2018. It was decided that a time component would be collected, but for the purposes of anonymity the responses would be categorized into a limited number of options, and only with a sufficient number of survey responses could the aspect of time be reviewed for whether there were differences in survey responses.

The final aspect of the survey questions that was considered during survey development was privacy. The type and length of professional experience was desirable since demographic data could be interesting, however a study participant’s name or current company affiliation was
not deemed necessary. The participant’s name was deemed private since one of the questions asked whether the individual believed that current resources were sufficient for a new regulator to make their first request. An individual who works for a business could feel uncomfortable answering ‘no’ in the survey if they believed that could be perceived negatively by the USDA - CVB. Furthermore, an individual’s experience was not necessarily acquired at the company they were currently affiliated with; therefore the company affiliation was pointless.

At the same time that the content of the survey was being developed, decisions were made for the format of the survey and the mode of communication. Written surveys could be non-electronic or electronic fillable surveys; delivered by postal mail, electronic mail, or web based survey applications. Non-electronic fillable surveys were identified as the least preferred since participants could hand write answers that might be more difficult to read compared to typed fonts, and postal mail was set aside due to the increased cost and decreased ease associated with delivery and return of the survey. Having settled on an electronic fillable survey, the final decision in communication form was to deliver it by electronic mail or a web based survey application.

In evaluating the first option to deliver the survey by electronic mail, there were various software possibilities evaluated. Unprotected word processing software options were deemed undesirable due to the ability of the respondent to alter the contents of the survey, and protected word processing software was undesirable due to the possible incompatibility across iOS devices that could be used to complete and return the survey. An Adobe Portable Document Format (PDF) fillable form was selected due to the likelihood that the software was already in use by respondents, or could be acquired free of charge by respondents. The audience that the survey was designed for included persons working at companies that were regulated by USDA – CVB.
according to the Veterinary Biological Products code book, or consultants to those companies. Individuals that submit documents to the USDA – CVB through the National Centers for Animal Health portal were expected to be accustomed to using PDF, since most documents submitted through the portal were this format, and for non-portal users, forms available from the USDA – CVB were commonly in PDF.

The second option was to deliver an electronic web based survey. Compared to a survey delivered by email, the ability to quickly complete the survey was expected to be no different. A web based survey would have the benefit of being able to transmit the survey results easily through the click of a button, and potentially (depending on the survey application used) an ability to direct the user to the desired questions based on their responses to previous questions. An added benefit to the survey creator could be an ability to analyze data, depending on the web based application that was selected. In researching web based applications, it was confirmed that applications existed to allow answers to be skipped, which was necessary to allow participants to choose not to answer a question at their discretion. Unfortunately, the main detriment to web based surveys was the desire for personal privacy or anonymity balanced against an ability to begin but not complete the survey in one sitting. In an effort to acquire openness in the responses, it was intended to disconnect the respondent from the completed survey and to create anonymity for the respondents. No personal information such as name, email address, or employer affiliation was to be collected. Some web based applications, such as Survey Monkey, allowed for anonymity in some forums, for example the survey creator could turn on anonymous responses with some exceptions, and could choose not to track IP addresses except when using certain data collectors. The detriment to using these methods of anonymity was that a respondent who had begun the survey would be required to complete and transmit the survey in
one sitting, because the survey responses could not be saved and attributed to the respondent to allow the respondent to complete questions later. This was an issue because one question in the survey was the number and type of communications required to achieve a decision of jurisdiction, which could be completed from a respondent’s memory or potentially required the survey to be set aside and completed after consulting records.

To allow users to set aside the survey while also not collecting personal information, the decision made was to use a fillable PDF that could be completed and transmitted via electronic mail and disconnected from the respondent manually.

Survey Validation

To validate the survey, a pilot study was performed in which the draft survey was reviewed by both personnel familiar and unfamiliar with requests for jurisdiction to evaluate if the questions captured the topic. Questions asked of participants included whether the survey was easy to understand or were there questions that were confusing, was the survey easy to complete, approximately how much time did it take to complete, did they think the survey was worth their time, were participants comfortable answering questions, did participants understand they could skip questions and were there any improvements suggested.

In this phase, the introduction to the survey was simplified based on negative feedback regarding the length. Within the introductory questions, where demographic information was collected, one suggestion was to define the term ‘Animal Health’. Conversely, the same person suggested the term was clear in that it was broad based on the answers that could be selected, and suggested reducing the length of the other questions or explanatory notes in the section. The latter suggestion was implemented to reduce the length of questions and explanatory notes in the section. Multiple people gave feedback that the questions with checkboxes and dropdown lists
were preferred over free text fields, either for clarity, for ease of completing the survey, or due to the potential intimidation to fill a large text box. As a result, the use of text fields was reduced by replacing them with choices selected by checkbox or dropdown list options in some cases, and the visual size of the remaining text fields was reduced, while applying no technical character limit on those fields. A free text field to provide further information at the discretion of the study participant was included as the final question in each survey section to accommodate additional information, and completion of this question was marked as optional. Finally, it was suggested that a phrase of caution should be removed, because the cautionary terms could discourage participation. The language suggested survey participants without formal experience should use their informal knowledge gained to date, before conversing with others in the matter, to allow the survey to capture only the participant’s knowledge. The suggestion to remove cautionary language was implemented on the basis that sufficient participation in the survey was a priority, and the caution could unintentionally bias the participant against identifying in a subsequent survey question whether they would choose to consult other people when writing a jurisdiction request.

In the process of survey validation, in determining if the survey was worth the time spent to complete it, participants provided their opinion whether questions were necessary. One person suggested the demographic information may not be necessary, however on the basis that the information would be interesting, no changes were made in the survey to remove demographics. One person suggested that two questions in the introductory assessment could be combined into a single, two-part question. This suggestion was not implemented, since one purpose of the two questions was to categorize the experiences of the respondents easily to determine whether blocking could be applied during data analysis, while the other question was
designed to direct the participant to proceed to the next applicable section of the survey. It was decided to keep the directional question separate. One person expressed concern that providing the time period of their first jurisdiction request could make it clear who completed the survey, in the event that there were few jurisdiction requests that particular year, therefore a note was added to the survey to explain the specific years would not be summarized in the results of the thesis. Finally, one person suggested the survey was repetitive when reviewing it as a whole, while another person commented that they could see how the survey was consistent in the subsections so that an answer from an experienced and an inexperienced individual could be collected separately and matched across the experience levels. No changes were made to the survey based on these comments, as the survey was designed in this way to allow for blocking by experience provided that sufficient responses were received from each experience level, and was designed to allow for no blocking in the event that few responses were received in one or more of the three experience level categories.

Survey Approval

The protocol for this study was determined to be exempt by the University of Georgia (UGA) Institutional Review Board (IRB) on March 27, 2018, identification number STUDY00005791, with provision to follow the requirements in the UGA Human Research Protection Program: Investigator Manual (HRP-103, revised April 2017). The IRB submission included a proposed draft electronic mail, consent letter and survey for review.

In order to transmit the survey via email in a consistent fashion, an introduction was written that could be utilized to send each survey with minimal modification. The initial survey introduction was revised based on feedback received during survey validation. The final version introduced the purpose of the survey, the scope of experience desired, a statement of permission
to forward the survey to others with experience, an estimation of time required to complete the survey, the deadline to complete the survey, and the preferred method of contact with any questions. The deadline to complete the survey was modified in each email based on the date the email was prepared, to allow participants at least two weeks to complete the survey. Copy of the survey introduction is available in Appendix A.

The consent letter was written using a standard template provided by The University of Georgia. The consent letter contained some of the information used in the email introduction, and communicated that participation in the study was voluntary. The letter described participants could choose to not answer one or more question in the survey, and answers to completed questions would be analyzed. For the purposes of confidentiality, identifiable information was not being collected; therefore as requested by the IRB, an option allowing study participants to print and mail the survey to the student or to provide answers via telephone was included. The letter described no guarantee could be made regarding the interception of data sent via the internet, explained how answers to questions would be combined with all other responses to present results in a summary form, and there was no direct benefit or monetary compensation by being a part of the survey. The letter described how individuals receiving the survey could request copy of the completed thesis, regardless of whether they chose to participate in the study. Lastly, contact information was provided in the event of questions, it was advised that participants were agreeing to participate if they returned the survey and it was advised that participants should keep the letter for their records. The date of the letter was modified with each date the survey was sent to potential study participants. Copy of the Consent Letter is provided in Appendix B, with the home address and phone number redacted.
The survey was written to contain four parts. All participants were asked four introductory questions to collect demographic information and experience level, and to direct participants to the next applicable portion of the survey. Individuals without experience making a request to CVB to determine the jurisdiction of a product were directed to Section C, where they were asked five prospective questions regarding what written and personnel resources they would use, what items they would include in a request, to whom they would submit the request, and whether they believed the resources available in the public domain were sufficient to make an effective request to CVB.

Study participants with experience were directed to Section A, where they were asked ten retrospective questions regarding the first time they made a request for jurisdiction to CVB. Similar to the questions in section C, they were asked what written and personnel resources they did use, what items they included, who they submitted the request to, and ultimately whether they believed the resources available in the public domain were sufficient to make an effective request to CVB. The additional questions in Section A that were relevant only to a person with actual experience were the time period of their request, the number of communications required before an assignment of jurisdiction was made, specifically what information did the CVB request in order to make a decision, was the jurisdiction assigned to CVB, and an optional question to share any further comments desired.

Study participants with three or more experiences were directed to Section A to advise on their first experience, and then were directed to complete an additional four questions in Section B to advise on their last or most recent experience. In section B, they were asked to rank the importance of written and personnel resources available, give prospective advice on which items they suggested to be included in a request for jurisdiction, to assess if they believed the resources
available in the public domain were sufficient for a new regulator, and an optional question to share any further comments desired. In this way, participants answered as many as nine, 14 or 18 questions based on their level of experience. Copy of the survey is provided in Appendix C.

**Statistical Analysis**

The survey was designed to allow for blocking of the data set provided at least five responses were received from what can be referred to as novice, experienced, and expert study participants with zero, one to two, or three or more requests for jurisdiction in their histories. In the event less than five responses were received in any category, the data would be combined for statistical power. It was determined that at minimum five surveys were needed to statistically analyze the results, and thus to block the data set at least five surveys were needed for each Section A, B and C of the survey. For example, if seven surveys were completed by persons without formal experience (Section C), 14 surveys were completed by personnel with experience (Section A), and among those 14 there were six surveys completed by personnel with significant experience (Section B), then the data would be blocked by experience and analyzed in three subparts (n = 7, 14, 6). This was to allow for an assessment of whether there were differences in opinions and experiences based on the experience level.

Alternatively, if two surveys were completed by persons without formal experience (Section C), 20 surveys were completed by personnel with experience (Section A), and among those 20 there were three surveys completed by personnel with significant experience (Section B), the data would not be blocked. In that case, all matched data would be combined to a single data set (n = 22), and due to the lack of statistical power with only three surveys completed in Section B, the questions of ranking and items that should be included in a request for jurisdiction would not be analyzed. The questions assessing if they believed the resources available in the
public domain were sufficient for a new regulator would be assessed to determine if it was matched with the answer provided in Section A such that it was unchanged and already captured in the combined data set, and the optional question to share any further comments desired would be combined with all the optional comments provided to determine if the minimum threshold of five comments was achieved to allow for a qualitative analysis to be performed.

The survey was designed to ask all respondents to provide their opinion for whether the resources were sufficient (Yes) or insufficient (No) for a new regulator to write an effective request for jurisdiction to the CVB. Experienced respondents were expected to form an opinion in the affirmative or negative. It was preferred that inexperienced respondents would also have an affirmative or negative opinion. However, in case an inexperienced respondent was not comfortable committing to one opinion, a third option (Not sure) was added for this subset of participants only. This neutral response was allowed for only novice respondents in an effort to encourage them to complete and return the survey. Inexperienced respondents had only five questions to answer regarding their prospective interpretation of the regulatory guidance available, therefore a concern raised during survey development was that an inexperienced respondent might not be comfortable making the affirmative or negative decision, and could be given an option that allowed them to not decide and make comments instead. This was to allow the study participant to still complete the survey and return it so that responses to the other questions could be analyzed. An alternative to allowing the neutral response option for an inexperienced respondent could have been emphasizing that participants could skip an answers they chose and still return the survey.

The statistical plan as stated earlier was to analyze the data within blocked groups based on experience level, or across all respondents if there were less than five responses in one or
more level of experience. The nominal data would be assessed either with or without blocking to calculate the percent frequency, $f_i / n * 100$ where $f_i =$ count of responses Yes / No and $n =$ total number of responses. The hypothesis would be supported if $H_a : f_{\text{No}} / n * 100 > f_{\text{Yes}} / n * 100$ and the null hypothesis would not be rejected if $H_0 : f_{\text{No}} / n * 100 \leq f_{\text{Yes}} / n * 100$. In the event of blocking, the frequency calculations would then be compared qualitatively.

Categorical data collected from supporting questions would be blocked as needed (depending on the number of responses per experience level) and analyzed through tabulation with frequency calculations to allow for the mode (most common response) to be identified. The time period identified for actual jurisdiction requests was expected to be transformed into categorical data centered around the 1982 and 2013 creation and revision of the Memorandum of Understanding between the USDA and FDA, and then only in the event of sufficient responses in each category ($n \geq 5$) would a secondary analysis be pursued with blocking based on chronological time to assess data trends. Secondary analysis would similarly include tabulation with frequency calculations.

Similar to categorical data, the numerical data collected would be tabulated with frequency calculations and an assessment of mode (most common response). In addition, the average and standard deviation would be calculated. The combined data would be analyzed, or blocking based on experience level would be applied prior to analysis if sufficient responses were received for each level of experience ($n \geq 5$).

**Survey Transmission and Collection**

Study participants were contacted directly and individually such that each recipient of the survey was not aware of other recipients receiving the survey, and therefore the emails were sent across multiple days. Recipients were asked to complete the survey by a specific date, which
was two weeks from the date of the email. The email sent to prospective study participants included language allowing the recipient to forward the survey to others or to provide the contact information of others who may have experience with jurisdiction requests. As surveys were transmitted and collected, in addition to receiving completed surveys, contact information was received and any request made to forward the survey to others was granted. Any new contact information received was added to the list of potential study participants and the survey was transmitted, again with a request to complete the survey within two weeks. In this way, the survey period remained open until at minimum two weeks had passed from the date of the last email transmitted with a survey.

As each survey was received, to protect the anonymity of respondents and help ensure blinding to the identity of the respondent, the survey was saved using the Adobe Acrobat function “Remove Properties and Personal Information” and in the advanced security settings the file owner attribute was reviewed and confirmed to be the survey creator. Upon receipt of each survey, the file was numbered in the order in which it was received. During survey collection the files were also printed to PDF (filename P01, P02, P03), in order to prevent the forms from being further edited. In a few cases where the free text typed by the respondent exceeded the space visible in the printed PDF, the text that was not visible was copied into a text field added to the page and the file was reprinted to PDF to prevent further editing.

Data Entry

The original plan was to enter the data as the surveys were received, and a quality check would be completed on closure of the survey period. On opening the first survey to perform this action, a concern was identified that entering the data immediately upon receipt could result in an unintentional mental connection being made between the survey participant and their responses.
This became a concern in the event the survey participant was personally known which could inadvertently bias the review of the data due to personal knowledge not reflected in the survey results. The qualitative analysis of comments made by survey participants could be subjective, so to help control against bias, the review of comments needed to be made on anonymous surveys. Based on this, the decision was made to hold all surveys for data entry at a later time and to mix the surveys so that the order in which the surveys were received would no longer be evident. By disconnecting the survey from the original order in which was received, the identity of the study participant could be anonymous. In retrospect, blinding through the use of another individual to enter the data, followed by double entry of data to quality check the data, could have improved this step in this study.

After closure of the survey period, the surveys were reviewed in PDF printed format to avoid any inadvertent revision of data. It was reconfirmed that all text was visible, and the original modifiable surveys were electronically deleted. Only the PDF printed versions were retained for data entry since the content of these surveys could not be edited. These surveys were then mixed four times using the Microsoft Excel random number generator “randbetween(1,100)”. For example, survey P01.pdf was renamed 35.pdf because the first randomly generated number was 35. In the first cycle, three randomly generated numbers were duplicated, for example one file was named 42.pdf and another was named 42 (2).pdf. Upon completion of the file renaming, the files were sorted numerically by name, and the second set of random numbers was generated. Two numbers were duplicated in the second cycle. The files were resorted numerically, the third set of random numbers was generated, and the files were renamed with two numbers duplicated in the third cycle. The files were resorted numerically, the fourth set of random numbers was generated, and the files were renamed with one number
duplicated. The files were resorted numerically for the last time, and were manually renumbered 01.pdf to 19.pdf since nineteen completed surveys were received.

Data from the surveys was entered into a Microsoft Excel file for analysis. Four worksheets were created, and data from the four sections of the survey were entered into the respective worksheet. The four survey sections represented demographic information, experience with one or more jurisdiction request, experience with three or more requests, and experience with zero requests. Any discrepancies across the data were noted at the time of initial data entry.

To quality check the data entry, the surveys were printed. Since the data was originally entered on a survey by survey basis, the quality check was performed on a page by page basis across the surveys, meaning page one was assessed across the surveys, then page two was assessed, and so on. Responses recorded in each worksheet were read aloud and the paper copies were highlighted to confirm the recorded answers on this page by page basis. As each Excel worksheet was verified, it was password protected to prevent any inadvertent editing. Three corrections were made during this process; one to transcribe the exact language used in one survey rather than paraphrasing as was done during the initial data entry, one to delete a “1” in the data where a checkmark had not been made in the survey, and one to correct the reason a person would be selected for consultation to match the paper copy of the survey. A copy of the spreadsheet was made, worksheet protection was removed from the copy, and data analysis was conducted on the unprotected copy. The electronically printed PDF surveys were retained while the hard copy printed surveys used to double check data entry were shredded. A secondary quality check was subsequently performed, using the electronic surveys to audit the electronic spreadsheet. No further corrections were necessary.
CHAPTER 4
RESULTS AND DISCUSSION

Response Rate

In preliminary research the population size was defined as 89 biologics companies regulated by USDA – CVB. This was based on the book “USDA Veterinary Biological Products Licensees and Permittees Prepared January 4, 2017”. As new companies emerge or existing companies merge, this number can fluctuate. In the book issued approximately eighteen months later, on July 5, 2018, the number of licensees and permittees with an address different from a licensee had decreased to 83 biologics companies.

Attempts were made to locate at minimum one person to receive the survey at each company. During this process, it was discovered that the original population estimate may have been inflated by a number of permittees. To clarify, permittees import products into the United States for distribution and sale, and a permittee may be associated with a licensee or it may be independent of a licensee according to the company names and addresses listed in the USDA Veterinary Biological Products book. To calculate the population size initially, any permittee associated with a licensee with the same address was connected to its licensee counterpart and therefore was counted as one licensee to be contacted. There were 13 permittees that were not associated with a licensee as of July 5, 2018. Most of these permittees were listed in the code book for the importation of one or two products, mostly diagnostic test kits or kit components or bovine IgG or antivenin. Twelve of these companies were successfully reached and declined to receive the survey, some of which shared they declined to take part because the jurisdiction of
their product was clear. One company was not contacted since the company name was new to the product licensee and permittee book at the time that the survey period was closing.

Attempts were made to locate at minimum one person to receive the survey at each company in the code book. There was no maximum limit for the number of people that could be contacted within a single company, since the survey requested an individual’s experience and interpretation regardless of the individual’s current employment or company affiliation. From the 83 companies in the code book, 13 permittees did not take part in the survey as previously described, and representatives from 17 licensees either did not respond or declined to provide an email address to take part in the survey. Among the remaining 53 licensees, plus organizations and consultants to these companies, there were 130 surveys distributed and 19 completed surveys received. This resulted in a response rate of 15%.

Nineteen surveys was one less than the desired sample size of 20 using a population size of 89 companies, confidence level 95%, at margin of error 20%. This was deemed to have no negative impact on the study because the number 89 companies was admittedly an imprecise estimate as described in Chapter 3, and was likely an overestimation of the population size. During preliminary research, it was reported that an average of one jurisdiction request was received per month. These 12 jurisdiction requests within a year could have been elicited from one to 12 companies, meaning not all 89 companies developed products that had an uncertain jurisdiction. The population of companies in need of submitting an effective request for jurisdiction was likely to be smaller than 89 companies based on both the estimated number of jurisdiction requests annually and the decrease in the number of biologics companies to 83 at the time of the survey. Twenty surveys were necessary at a 95% confidence interval and 20% margin of error to assess sample from a population size of 88 – 114. Nineteen surveys were
necessary under the same confidence interval and margin of error to adequately sample from a
population size of 69 – 87,\textsuperscript{37} which was likely to be closer to the population size given that there
were only 83 unique biologics companies listed in the book of licensees and permittees at that
time.

The statistical analysis plan allowed for the blocking of data based on three levels of
experience, provided that a minimum sample size $n \geq 5$ was achieved within each data block
among the 20 or more surveys received. Data blocking was not performed since the sample size
$n \geq 5$ was achieved in only one category of experience. Four surveys were received from
individuals who did not have formal experience, 12 surveys were received from people with one
or two experiences, and two surveys were received from people with three or more experiences.
As a result, the 19 surveys were combined for data analysis. Since the statistical analysis plan
allowed for subset analysis of data blocks as little as $n = 5$, it was determined that receiving 19
surveys as opposed to 20 had no impact on the results of the study.

**Demographics**

As previously described, in order to achieve the desired sample size among the small
population of biologics companies regulated by USDA – CVB, the survey was sent to employees
of the companies and also to animal health organizations and consultants to the companies.
There was no maximum limit for the number of people that could be contacted within a single
company. Due to the pool of companies being small, it was assumed that personnel contacted
for the survey may have gained experience in jurisdiction requests at either their current or any
one of their former employers; therefore choosing to contact only one individual at a larger
company where multiple individual email addresses were located would have been an
unnecessary restriction to the data set. Conversely, by contacting as many people as could be
found, it was possible that more than one person completed a survey that represented a single jurisdiction request. Since the fundamental question was one of interpretation in whether the acts, laws, regulations and guidance available were sufficient for a jurisdiction request to be made, it was possible that two individuals working on the same jurisdiction request could have the same or different answers to this question. As a result, no analysis was deemed necessary to identify whether multiple individuals were reporting on the same jurisdiction request, and the survey was not designed to collect the level of detail required to do so.

The type and total length of professional experience in the animal health sector was collected in this study. The type of experience is summarized in Table 1 and shows that most survey participants were employed by companies, as would be expected since a list of companies was the foundation to develop the list of prospective study participants. The type of professional experience did not sum to 100%, since an individual could have employment experience in more than one category.

Table 1: Type of professional employment experience

<table>
<thead>
<tr>
<th>n = 19</th>
<th>Private Practice</th>
<th>Consultant</th>
<th>Membership Organization</th>
<th>College or University</th>
<th>Company</th>
<th>Government Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabulated (#)</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>5%</td>
<td>16%</td>
<td>0%</td>
<td>5%</td>
<td>95%</td>
<td>11%</td>
</tr>
</tbody>
</table>

All study participants reported at least eleven years of professional experience in the animal health sector (Table 2). Most had eleven to twenty years of experience, indicating participants were likely to be knowledgeable about the animal health industry.

Table 2: Length of professional experience in the animal health sector

<table>
<thead>
<tr>
<th>n = 19</th>
<th>≤ 5 years</th>
<th>6 – 10 years</th>
<th>11 – 20 years</th>
<th>21 – 30 years</th>
<th>≥ 31 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabulated (#)</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>0%</td>
<td>0%</td>
<td>58%</td>
<td>16%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Among the 19 participants, 21% had no formal experience making a jurisdiction request, 63% had experience in one or two requests, 11% reported experience in three or more requests, and one participant (5%) did not respond to the question. One design consideration in the survey was participants completed various sections of the survey based on the number of jurisdiction requests in their experience. If at least five responses were received in each category of experience, then blocking would have applied to analyze the data within these sub-groupings. Since the minimum number was not met for the formally inexperienced (zero jurisdiction request) or highly experienced (three or more jurisdiction request) categories, blocking was not applied and data from the 19 surveys was analyzed collectively. The ranking of resources collected from highly experienced survey participants was not assessed due to the minimum threshold not being met. Similarly, there was no comparison made of the items included in an individual’s first jurisdiction request versus their last (or most recent) request to assess whether the items changed over time. Since the survey did not collect data to consider causation, such as changes in requirements versus changes in experience level, these results could have been interesting but were not critical to assess the null hypothesis. The comments from formally inexperienced and highly experienced individuals were assessed, since they were combined with comments from the rest of the surveys to meet the minimum threshold of five responses to allow for analysis.

To analyze the data collectively, the results from two sections of the survey were combined. The survey was designed to allow for this type of analysis. Specifically, one section was written for participants with experience to retrospectively answer questions, while one section was written for participants without formal experience to prospectively answer matched
questions. The combined data is described in the past tense, with acknowledgement that the prospective answers collected were technically written in future tense in the survey tool.

**Resources**

The survey included a question requesting the time period of the study participant’s first jurisdiction request in terms of year. This data was categorized into three time periods centering on the Memorandum of Understanding between the USDA and FDA, meaning pre-1982, 1982 to 2012, and 2013 to present. If the data showed sufficient information to allow blocking by time period, then a secondary analysis was planned to assess whether interpretations had changed over time. For example, if survey participants submitted requests pre-1982 and interpreted the requirements as being unclear, but participants making jurisdiction requests in 2013 interpreted the requirements as being clear, then a case could be made that the current requirements are clear.

In this research, there was insufficient response in the “pre-1982” and the “2013 to present” categories to allow for meaningful statistical analysis; therefore the secondary analysis was not performed. Since the secondary analysis was not performed, the data collected regarding the written resources people used was collapsed accordingly. For example, when a study participant identified they consulted the Virus-Serum-Toxin Act of 1913 and/or the Virus-Serum-Toxin Act of 1985, this was normalized to one entry for the Virus-Serum-Toxin Act.

Most people surveyed used Title 9 of the Code of Federal Regulations, the Virus-Serum-Toxin Act and the Memorandum of Understanding to write a jurisdiction request, as summarized in Table 3. It was not surprising that Center for Veterinary Biologics Notice 05-07 was referenced as a resource used by only four people surveyed, since that notice was specific to vaccines to reduce or eliminate bacterial colonization in animals. The use of a company
example, meaning a written record of a previous request made by another person at the company, was also identified by four people. Three people identified another document was used, and it was interesting that all three respondents identified the resource was provided by individuals at CVB, such as a written description or presentation given by CVB personnel. Finally, the Office of Science and Technology Policy “Coordinated Framework for the Regulation of Biotechnology” was the least used resource, which was reasonable given that it was not found linked to the USDA – CVB website for biologics regulations and guidance. In summary, there were certain written resources used by most survey participants, with Title 9 of the Code of Federal Regulations being most common (89%), however no single resource was identified by all 19 participants. This indicated that in lieu of having a guidance document to follow from the CVB to direct how to write a request for jurisdiction to the CVB, there was a common instinct by personnel in industry to consult the regulations, the Virus-Serum-Toxin Act and the Memorandum of Understanding between the agencies.

Table 3: Written resources

<table>
<thead>
<tr>
<th>n = 19</th>
<th>Tabulated (#)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title 9, Code of Federal Regulations</td>
<td>17</td>
<td>89%</td>
</tr>
<tr>
<td>Virus-Serum-Toxin Act</td>
<td>14</td>
<td>74%</td>
</tr>
<tr>
<td>Memorandum of Understanding Between USDA &amp; FDA</td>
<td>13</td>
<td>68%</td>
</tr>
<tr>
<td>Center for Veterinary Biologies Notice 05-07</td>
<td>4</td>
<td>21%</td>
</tr>
<tr>
<td>Company Example</td>
<td>4</td>
<td>21%</td>
</tr>
<tr>
<td>Other Document (specify): Resources Provided by CVB</td>
<td>3</td>
<td>16%</td>
</tr>
<tr>
<td>Office of Science and Technology Policy Coordinated Framework</td>
<td>2</td>
<td>11%</td>
</tr>
</tbody>
</table>

In every survey, participants identified at least one person that they consulted before sending their first jurisdiction request. Study participants were given a list of options and reasons for those options, as well as allowed to identify an additional person and reason not previously described.
The raw data is described in Table 4. Most people surveyed consulted an individual in the Center for Veterinary Biologics – Policy, Evaluation and Licensing (CVB-PEL) (18/19 or 95%). Over half of the survey participants also consulted a colleague in the company where they worked (11/19 or 58%). The survey allowed for users to add another person and to add in free text any reasoning, or to identify that no people were consulted; these choices were not selected. Since there were a number of reasons to consult personnel that were not selected, only the reasons that were chosen are summarized graphically in Figures 1 and 2.

Table 4: People consulted with reasoning

<table>
<thead>
<tr>
<th>Reason</th>
<th>Tabulated (#)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A colleague in the company where you worked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I reported to them</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I knew they had this experience</td>
<td>10</td>
<td>53%</td>
</tr>
<tr>
<td>I had worked with them in the past</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I respected their opinion in general</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>I knew them personally</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>A person at another company (e.g. contractor, consultant)</td>
<td>2</td>
<td>11%</td>
</tr>
<tr>
<td>The company had a contract with the person</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I had worked with them in the past</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I knew they had this experience</td>
<td>2</td>
<td>11%</td>
</tr>
<tr>
<td>I respected their opinion in general</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I knew them personally</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>The CVB – Policy, Evaluation and Licensing</td>
<td>18</td>
<td>95%</td>
</tr>
<tr>
<td>They were assigned to the company as a reviewer</td>
<td>9</td>
<td>47%</td>
</tr>
<tr>
<td>They were listed on the Memorandum of Understanding</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I had worked with them in the past</td>
<td>2</td>
<td>11%</td>
</tr>
<tr>
<td>I respected their opinion in general</td>
<td>5</td>
<td>26%</td>
</tr>
<tr>
<td>I knew them personally</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>No reason selected</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>A person not listed above (describe)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>I did not consult any people</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

As shown in Figure 1, most people surveyed consulted an individual in the Center for Veterinary Biologics – Policy, Evaluation and Licensing (CVB-PEL). Over half of these survey participants also consulted a colleague. Whether they consulted a colleague within their own
company or a colleague at another company (such as a contractor or a consultant), the reasoning was because the study participant knew someone else had experience in a jurisdiction request written to the CVB.

Figure 1. People consulted for information on how to write or submit a jurisdiction request

The reasons for choosing to consult an individual at the CVB were by necessity different from the reasons to consult an individual within a company; therefore the reasons to consult CVB-PEL are depicted also in Figure 2 for further discussion. The most common reason to consult the CVB-PEL was the person was assigned to the company as a reviewer (9/18 or 50%). Another major reason to consult CVB-PEL was out of respect for their opinion in general (28%). Other reasons selected were due to working with the CVB-PEL person in the past, or knowing them personally. In one case, no reason was selected.
Submissions to the CVB

There appeared to be a high level of variability regarding who jurisdiction requests were sent to within the CVB; however this was due to a weakness in the design of this survey question. No one selected an individual in the CVB – Inspection and Compliance (IC) section, which was reasonable since a question regarding licensing ability would logically be sent to CVB personnel within or with oversight to the Policy, Evaluation and Licensing (PEL) section of the agency. One survey participant specifically wrote in that they submitted their request to the CVB-PEL Director, which highlighted a weakness in that the survey did not specify an easy option to select this position. The CVB-PEL Director oversees the Policy, Evaluation and Licensing section, while the CVB Director is a level above responsible for both the PEL and IC sections. If it were assumed that participants selected “CVB Director” with the intention that this meant “CVB-PEL Director”, then 3/19 (16%) submitted their request to the CVB-PEL Director, 4/19 (21%) submitted their request to both the CVB-PEL Director and the CVB-PEL reviewer.
assigned to the company, and 10/19 (53%) submitted the request to the CVB-PEL reviewer assigned to the company.

In this best case scenario, a total of 14 participants chose to include the CVB-PEL reviewer assigned to the company (74%) and seven included the CVB-PEL Director (37%). Two respondents (2/19 or 11%) submitted their request to the CVB-PEL reviewer identified on the Memorandum of Understanding (MOU) between USDA and FDA. In the worst case scenario, the requests for jurisdiction were sent to one or more people, among five possibilities selected, and only 53% of participants were aligned that the request was to be sent to the CVB-PEL reviewer assigned to the company. This identified a second weakness in this survey question: the survey asked who the first jurisdiction request was sent to, which allowed four participants to select both the CVB Director and the CVB-PEL reviewer assigned to the company. This answer was sound since it is possible to send correspondence to one person as the primary recipient and to one or more other persons in courtesy copy. Ideally the survey would have asked participants to select the one person that their first jurisdiction request was primarily directed to, so that it could be determined if these participants primarily sent their request to a Director level (3/19 to 7/19 or 16% - 37%) or to a Reviewer level assigned to the company (10/19 to 14/19 or 53% - 74%). Sending 16% of jurisdiction requests to the Director, 74% to the Reviewer assigned to the company, and 11% to the Reviewer on the MOU could indicate it is fairly clear that requests should be directed to the reviewer. Conversely, sending 37% of requests to the Director, 53% to the company Reviewer, and 11% to the MOU Reviewer could indicate a lack of clarity. The survey answers as collected without transformation are presented in Figure 3. My interpretation of the data is that it is sufficiently clear that CVB-PEL (as opposed to CVB-IC) should receive requests for jurisdiction, and the reviewer assigned
to the company most commonly received these requests historically, with higher level CVB-PEL included or in lieu of the assigned reviewer, at the discretion of the person submitting the request. Since there were two cases in which the interpretation was to submit the request for jurisdiction to the CVB-PEL reviewer listed on the Memorandum of Understanding, it could be useful to industry to receive clarity from the CVB as to whether this is the individual the CVB prefers to receive jurisdiction requests.

Figure 3: Personnel to which jurisdiction requests were sent

During this research, it was of interest to understand precisely what to include in a request for jurisdiction. When developing the survey, my interpretation was there was uncertainty as to what information should be included in a request for jurisdiction. By not knowing what was important, practically every item that could be thought of was included in the survey. To account for items that had not been considered, an option was included to provide additional items that were not identified, and to describe them. Zero survey participants suggested additional items.
It was striking that more than half of the survey participants selected ten of the options provided, as shown in Figure 4, and not one item was selected by all 19 participants. Most of the survey participants included the composition of the product, the product’s intended use to diagnose / cure / mitigate / treat or prevent disease in animals, the species the product was to be administered to, and a statement that the primary mechanism of action was immunological (18/19 or 95%). Most participants provided the proposed product label claims, a description of how the product was made or manufactured, or a request that the jurisdiction be assigned to USDA-CVB (84 – 89%).

Figure 4: Items included in the first jurisdiction request

<table>
<thead>
<tr>
<th>Items Included (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 2 4 6 8 10 12 14 16 18 20</td>
</tr>
<tr>
<td>Product composition</td>
</tr>
<tr>
<td>Product manufacture</td>
</tr>
<tr>
<td>VSTA classification</td>
</tr>
<tr>
<td>Label claim</td>
</tr>
<tr>
<td>Intended use</td>
</tr>
<tr>
<td>Species</td>
</tr>
<tr>
<td>Administration route</td>
</tr>
<tr>
<td>Immunological mechanism statement</td>
</tr>
<tr>
<td>Experimental data for mechanism</td>
</tr>
<tr>
<td>Comparison to other product</td>
</tr>
<tr>
<td>Scientific literature or reference</td>
</tr>
<tr>
<td>Request jurisdiction assignment to CVB</td>
</tr>
<tr>
<td>Permission to share with FDA-CVM</td>
</tr>
</tbody>
</table>

Many survey participants identified they supplied experimental data supporting the primary mechanism of action was immunological (14/19 or 74%), indicating that four
individuals surveyed may have made a statement regarding the mechanism of action without providing experimental data directed towards this parameter. The mechanism of action could have been indirectly supported in other ways, for example 68% (13/19) of people described or classified that the product was a virus / serum / toxin or analogous product, 47% (9/19) included relevant scientific literature or references, and 11% (2/19) compared the proposed product to another product regulated by USDA-CVB.

Finally, 68% (13/19) identified the planned route of administration, and 32% (6/19) included permission to share their information with the FDA – CVM. In summary, ten of the 13 items included in the survey were identified by over half the study participants as being included in the first request for jurisdiction submitted to CVB. Scientific literature or references, permission to share with the FDA, and a comparison to another product were the only items that were chosen by fewer than half of the participants.

Communications with CVB

As described previously, 19 surveys were received from participants with various levels of experience ranging from zero formal requests for jurisdiction to three or more requests. Since the minimum number of surveys from inexperienced and highly experienced personnel were not received (n ≥ 5), the data was not blocked by experience level and the combined data from the surveys was analyzed as described above, with the caveat that both prospective and retrospective responses were described in the past tense. In this section, the number of surveys analyzed is n = 15 on the basis that 15 surveys were completed by individuals with experience making one or more jurisdiction request. Experiences related to the individual’s first request for jurisdiction is described here.
In seven cases, no questions were raised (7/15 or 47%) and the jurisdiction assigned was USDA – CVB. There were questions in approximately half of the cases (8/15 or 53%), and more than one item could be selected to identify the type of information that was requested.

Experimental data (or additional experimental data) was requested to support the primary mechanism of action was immunological in 6 cases (6/15 or 40%). This value included one free text response indicating more information was needed on the mechanism of action. Although 95% of survey participants identified they provided information regarding product composition in their jurisdiction request as shown in Figure 4, the composition of the product was required or it required further detail in four cases as shown in Figure 5 (4/15 or 27%).

Figure 5: Classification of USDA-CVB requests for additional information

Only six people surveyed identified they included permission to share their information with the FDA – CVM according to Figure 4, and yet in only three cases did the CVB formally request permission to share information with the FDA – CVM as shown in Figure 5 (3/15 or 20%).
20%). This indicates that the need to explicitly identify the USDA – CVB has permission to share information with the FDA – CVM was not necessary in all cases. Finally, the proposed product label claim was required (or required further detail) in two instances (2/15 or 13%) and an additional item, specifically a meeting, was requested once (1/15 or 7%). A description of how the product was made, or further detail to this effect, was not requested in any cases.

Ultimately, the jurisdiction for the product was assigned to USDA – CVB in most cases for the respondents to this survey (13/15 or 87%). Jurisdiction was decided as FDA in one case and no decision was made in one case.

Of the 15 survey participants that had experience submitting one or more jurisdiction request to the CVB, the number of communications and the nature of additional information requested by CVB were expected to be the more difficult questions for survey participants to answer, as this required a specific recollection of events or the consultation of records throughout the jurisdiction request, some of which lasted years. One person clearly identified they declined to respond to this question (1/15 or 7%), which identified a weakness in the survey. The survey was designed with a drop down box to select the number of communications from, however the default was designed as “0” instead of a placeholder such as “--”; therefore a true response of 0 could not be differentiated in the data from a lack of response, except that the individual who skipped the question commented as such. Despite this weakness, the data was analyzed as reported.

At minimum one formal submission for jurisdiction would be expected in every case, and only one formal submission was identified as required in nine cases (9/15 or 60%). A second formal submission was required in three cases (3/15 or 20%), while surprisingly five or more formal submissions were required in two cases (2/15 or 13%) as shown in Figure 6. The use of
scheduled teleconferences or meetings in person followed a similar pattern to the number of formal requests for jurisdiction. Most commonly, one meeting was employed (7/15 or 47%) and sometimes two meetings were necessary (4/15 or 27%). Five or more meetings by telephone or in person were necessary in two cases (13%).

Electronic mail was used as a form of communication in eight cases (8/15 or 53% in total for one to three emails), however unscheduled telephone calls were used infrequently (2/15 or 13%, both requiring five or more telephone calls).

Figure 6: Approximate number of communications with CVB during one request

<table>
<thead>
<tr>
<th>Number of Communications</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or no response</td>
</tr>
<tr>
<td>Formal</td>
</tr>
<tr>
<td>Email</td>
</tr>
<tr>
<td>Scheduled calls / meetings</td>
</tr>
<tr>
<td>Unscheduled calls</td>
</tr>
</tbody>
</table>

The type of information requested by the CVB during the review of a request for jurisdiction, and the number of communications exchanged between the survey participant and the agency, was of interest because increases in the number of these items supported an interpretation that further guidance from the CVB could be useful. There were questions in only eight of 15 cases, which could indicate that approximately half of the requests for jurisdiction
were effective. In five of 15 cases, which is one-third of the requests, at least two formal submissions to the CVB were required before the jurisdiction could be assigned.

**Survey Participant Interpretations**

One of the last questions asked in each section of the survey was whether the survey participant believed the resources available in the public domain were sufficient for a new regulator to make a request. Of the 19 respondents, five identified the resources were sufficient (26%) and 14 identified the resources were not sufficient (74%). The data was not blocked for experience level since fewer than five responses were received in the inexperienced and highly experienced categories. The highly experienced individuals with three or more jurisdiction requests answered this question consistently for their first experience and their last experience; therefore their responses were accounted for in their response to their first experience.

**Statistical Analysis**

The hypothesis of this research was the acts, laws, regulations and guidance available from USDA – CVB were insufficient to enable an individual to write a successful request for jurisdiction to USDA – CVB. The null hypothesis was therefore that the acts, laws, regulations and guidance were sufficient. All survey respondents provided their opinion for whether the resources were sufficient (Yes) or insufficient (No); therefore the percent frequency across all respondents was calculated using the nominal data as follows:

1. \[ \frac{f_i}{n} \times 100 \] where \( f_i \) = count of responses Yes / No and \( n \) = total number of responses
2. \[ \frac{f_{Yes}}{n} \times 100 = \frac{5}{19} \times 100 = 26\% \]
3. \[ \frac{f_{No}}{n} \times 100 = \frac{14}{19} \times 100 = 74\% \]

To support the alternate hypothesis that the acts, laws, regulations and guidance were insufficient, the percent frequency of No responses needed to be greater than the percent
frequency of Yes responses (H_a: f_{No} / n * 100 > f_{Yes} / n * 100). In this study, the alternate hypothesis was supported (H_a: 74% > 26%) to indicate the available guidance was deemed insufficient. The null hypothesis was not supported but also was not rejected by supporting the alternate hypothesis.

Tabulations with frequency calculations for the categorical data were discussed previously in Chapter 4, and are not reiterated here. The mode (most frequent response) from this data showed Title 9 of the Code of Federal Regulations was the most commonly used written resource and the CVB – PEL was most commonly consulted for further information. Requests for jurisdiction were most frequently submitted to the CVB – PEL reviewer assigned to the company, and there were four items most commonly included in these requests: (1) the composition of the product, (2) the product’s intended use to diagnose, cure, mitigate, treat or prevent disease in animals, (3) the species the product was to be administered to, and (4) a statement that the primary mechanism of action was immunological. During the first request for jurisdiction made by survey participants with experience, the most common response was CVB requested no additional information.

The number of communications required during a jurisdiction request was presented as a stacked bar graph, and the mode, average and standard deviation in the sample are summarized in Table 5. Unscheduled telephone calls were the least preferred method by the person submitting the request for jurisdiction, and zero unscheduled calls were made by 13 of 15 respondents. Unscheduled calls showed the greatest statistical disparity in responses, with the highest standard deviation at 1.76, because there was a mode of 0 but there were two responses of 5 or more calls (recorded as 5 for statistical analysis) which drew the average away from the mode to 0.67.
Table 5: Statistical summary of communications with CVB

<table>
<thead>
<tr>
<th></th>
<th>Formal submissions</th>
<th>Electronic mail</th>
<th>Scheduled calls or meetings</th>
<th>Unscheduled calls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 15</strong> Mode</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>1.67</td>
<td>1.13</td>
<td>1.67</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Standard Deviation</strong></td>
<td>1.45</td>
<td>1.30</td>
<td>1.50</td>
<td>1.76</td>
</tr>
</tbody>
</table>
CHAPTER 5

CONCLUSION

Conclusion and Recommendations

The purpose of this research was to determine if the information available in the public domain was sufficient for an individual to write a successful request for jurisdiction to USDA – CVB. Research included the review of historical information describing jurisdictional guidance, questions or issues faced by companies, and assessments or articles available in the public domain describing jurisdiction under the VSTA. The historical and current regulations and guidance available from the USDA – CVB was reviewed. Based on the review of literature, it was concluded that guidance directing industry on how to write a request for jurisdiction to the USDA – CVB was not available. While the definition of a biological product in Title 9 of the Code of Federal Regulations was helpful, and examples of biological products under USDA and FDA jurisdiction in the 2013 version of the Memorandum of Understanding between the agencies provided some further insight, a common theme from various authors in other reports and publications concurred that the pathway to determine jurisdiction of a product could be confusing to product developers.

The hypothesis of this research was therefore that the acts, laws, regulations and guidance available from USDA – CVB were insufficient to enable an individual to write a successful request for jurisdiction to USDA – CVB. A survey was conducted to collect the experiences and opinions of others in order to accept or reject the research hypothesis. In this study, the hypothesis was supported as most survey participants responded that the acts, laws, regulations
and guidance were insufficient for an individual to write a successful request for jurisdiction to USDA – CVB ($H_a: 74\% > 26\%$).

Although the hypothesis of this research was supported, indicating additional guidance from the CVB was necessary, the supporting data collected in this study was analyzed to lend some visibility as to what is already clear versus what is less clear to industry. In an effort to avoid confirmation bias, the data was evaluated for trends and the mode identified in the results is summarized. The most frequent responses given by study participants could indicate that there were aspects of a jurisdiction request that were clear, even if survey participants did not interpret them to be clear.

Assuming the survey participants are representative of the industry, it appeared from these results that the regulations in Title 9 of the Code of Federal Regulations, the Virus-Serum-Toxin Act, and the Memorandum of Understanding Between USDA and FDA were useful resources available to regulatory personnel employed by companies. It was also clear to submit the request for jurisdiction to a member of CVB – PEL. The most common response provided by survey participants was that no additional information was requested, and the jurisdiction assigned to the product was ultimately USDA – CVB, indicating a request for jurisdiction written to USDA – CVB was successful in most cases. Four items most commonly included in the requests for jurisdiction submitted by study participants were (1) the composition of the product, (2) the product’s intended use to diagnose, cure, mitigate, treat or prevent disease in animals, (3) the species the product was to be administered to, and (4) a statement that the primary mechanism of action was immunological. Also included by more than half the study participants, in the order of decreasing frequency, were (5) the proposed product label claims, (6) a description of how the product was made or manufactured, (7) a request that the jurisdiction be
assigned to USDA – CVB, (8) experimental data supporting the primary mechanism of action was immunological, (9) a description or classification that the product was a virus, serum, toxin or analogous product, and (10) the planned route of administration.

The need for additional guidance from the CVB was supported by the survey result that the CVB – PEL was often consulted (95% of survey responses), as were colleagues with prior experience, to help clarify how to write or submit a jurisdiction request. The use of persons as resources to supplement the written resources available was reiterated among the free text comments provided by study participants (5/10). In summary, the comments suggested talking to colleagues with prior experience and talking to the CVB, following instructions provided by CVB directly or through industry meetings, and communications with CVB were helpful. Although there were many cases in which no additional information was requested by the USDA – CVB (7/15), there were a number of cases in which further information was necessary. Specifically, experimental data (or additional experimental data) was requested to support the primary mechanism of action was immunological (6/15). Free text comments also identified the importance of the mechanism of action in a request for jurisdiction (2/10). Ultimately, while one formal submission resulted in a decision for jurisdiction in many cases (9/15), it was noted that a scheduled call or meeting was also necessary in many cases (7/15).

The recommendation based on this research is that a guidance document from the CVB instructing industry on what to include in a request for jurisdiction is necessary. It seems that since there is no CVB guidance to industry currently, it is common for industry to consult with personnel at CVB – PEL. Individual consultations can result in useful guidance to that individual or company, but that does not add to the knowledge base of others in industry.
Participants in this study experienced some instances of success in writing a request for jurisdiction, and many others experienced various requests for additional information from the CVB, indicating that industry was not able to provide successful requests consistently. There was some implication that the information necessary to support the mechanism of action as immunological was a common weakness. Guidance to industry as to what experimental data or what level of detail was necessary could have been helpful in those cases.

There were some obvious shortcomings in this study, most particularly in the number of survey responses received and the depth of the questions. If a follow up study were to be performed, collaboration with an industry organization could improve the response rate so that more specific details into the type of information submitted and the nature of the feedback received from the regulatory agency could be evaluated. In this first study, information regarding what occurred during jurisdiction requests was collected, but the deeper questions to rank importance was not analyzed due to the number of responses.

Collaboration with the CVB in a follow up study would be ideal, since the CVB would have the best insight into weaknesses in jurisdiction requests that have been submitted by industry. However, collaboration with CVB requiring any specific details would not be possible, since the information submitted by industry would be confidential business information. As a result, the desirable next step is not to conduct a follow up study, but instead to collaborate with industry organizations. These organizations could seek specific input from its membership to determine if guidance for jurisdiction requests is desired, and could then effectively work with CVB towards that guidance.
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APPENDIX A

Survey Introduction via Electronic Mail

Email Subject:
Thesis re: Jurisdiction Requests to USDA-CVB

Email Body:
Hello,

My name is Julie Hellstrom, and I am a student at the University of Georgia, working on a master’s degree in Regulatory Affairs. For my thesis, I am surveying people to understand their experiences with jurisdiction requests to the United States Department of Agriculture (USDA) – Center for Veterinary Biologics (CVB).

If you have experience in the research, drafting or preparation of a jurisdiction request to USDA-CVB, or the submission of the request, the communication with CVB, or receiving the response from CVB, then I would like to hear from you.

If you do not have this experience, but you have an opinion that you would like to share, then you can also take part in this survey.

If you know of other people with these experiences, please feel free to forward this survey to them or to send their contact information to me.

The survey is estimated to require 10 – 20 minutes to complete. If you are interested in completing this survey, please save the consent form for your records and complete the survey attached. Please complete the survey by July 1.

Please feel free to contact me at jhellstr@uga.edu if you have any questions, would like to complete the survey but need more time, or would like to request a telephone call.

Thank you,

Julie Hellstrom
APPENDIX B

Consent Letter

June 17, 2018

Hello,

I am a student in the Department of Pharmacy at The University of Georgia. I invite you to participate in a research study entitled “Jurisdiction requests to USDA-CVB for the regulation of biological products for animals in the United States”. The purpose of this study is to gather information regarding the knowledge and experiences of people who have been involved in jurisdiction requests to USDA-CVB. The results of the survey will be collected and summarized for the purposes of my thesis.

To participate, you must be 18 years of age or older, and you must be able to read and understand English.

Your participation will involve completing a written survey and should only take about 10 – 20 minutes. Your involvement in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. If you choose to not answer one or more questions on this survey, your answers to completed questions will be analyzed.

For the purposes of confidentiality, identifiable information such as your name or email address will not be collected as part of this survey. When you submit your survey, it will be received and downloaded into an electronic storage area with all other surveys. The document properties will be reviewed to ensure there is no identifying information present. Since there will be no individual identifying information used, you may return the survey via email to jhelistr@gvsu.edu as described in the survey, you may print it and mail it with no return address to Julie Hellstrom or you may provide your answers via telephone to [Redacted].

Your confidentiality will be maintained to the degree permitted by the technology used. Specifically, no guarantees can be made regarding the interception of data sent via the Internet by any third parties.

Your answers to completed questions will be combined with all other responses, and the results of the research study will be presented in a summary form only as part of my thesis. There is no direct benefit to participants. The findings from this research may provide information on the knowledge and experiences of people who have been involved in jurisdiction requests to USDA-CVB, which may help individuals who do not have this knowledge or experience.

There is no monetary compensation for the completion of this survey. If you would like to request a copy of the summary of the results, then you may request this by sending an email to jhelistr@gvsu.edu with the subject line “Send me a copy of your thesis”. You may request this regardless of whether you complete the survey, and your email address for this purpose will be recorded into a list that is sorted alphabetically each time a new email address is added. In this way, there will be no relationship between your email address and the order in which your request was received, and no relationship between your email address and whether you completed the survey.

If you have any questions about this survey, please feel free to contact me at jhelistr@gvsu.edu to communicate your message via email or to request a telephone call. Questions or concerns about your rights as a research participant should be directed to The Chairperson, University of Georgia Institutional Review Board, 609 Boyd GSRC, Athens, Georgia 30602; telephone (706) 542-8199; email address irb@uga.edu.

Thank you for your consideration, and please keep this letter for your records.

Sincerely,

Julie D. Hellstrom
APPENDIX C

Survey

This survey is divided into Sections based on your previous experience, so you are asked to complete only the applicable sections of the survey. The survey is estimated to take 10 – 20 minutes. Completion of this survey is optional.

Please begin with the Introductory Assessment questions, which will direct you to the next Section applicable to you.

<table>
<thead>
<tr>
<th>Introductory Assessment (4 questions)</th>
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</table>

1. What type of professional experience do you have in Animal Health? **Choose ALL that apply.**
   - [ ] Private practice veterinary
   - [ ] Individual consultant / employed by a consultant company
   - [ ] Employed by a membership organization (such as AHL, AVBC, AVMA, etc.)
   - [ ] Employed by a college or university
   - [ ] Employed by a company
   - [ ] Employed by a government agency

2. In total, approximately how long have you worked professionally in Animal Health? **Choose one.**
   - [ ] Up to 5 years
   - [ ] 6 – 10 years
   - [ ] 11 – 20 years
   - [ ] 21 – 30 years
   - [ ] 31 years or more

3. Do you have experience(s) in making a jurisdiction request to USDA-CVB? **Choose one.**
   NOTE: Experience includes researching, drafting, preparing, or submitting a request, communicating with the agency, or receiving the response from the agency.
   - [ ] Yes, I have been involved in making at least one jurisdiction request to USDA-CVB
   - [ ] No, I do not have this experience – please select “0” on the next question.

4. One jurisdiction request to USDA-CVB begins with the initial request submitted to CVB and ends with the final decision for jurisdiction (or cancellation of the request for jurisdiction).
   With this definition, how many jurisdiction requests to USDA-CVB have you been involved in?
   - [ ] 0 – please proceed to **Section C.**
   - [ ] 1 to 2 – please proceed to **Section A.**
   - [ ] 3 or more: please select the total number here: ___ – please proceed to **Section A.**
Section A (10 questions)

Please complete this section only if you have experience in making at least 1 jurisdiction request to USDA-CVB. (If you do not have experience, skip to Section C.)

Please complete this section to describe the FIRST time you made a request for jurisdiction to USDA-CVB. Please only describe your FIRST experience in this section.

A1. Other than people, what RESOURCES did you use for information regarding how to write or submit your FIRST jurisdiction request to USDA-CVB, before it was sent? Choose ALL that apply.

- [ ] Virus Serum Toxin Act of 1913 (Public Law 430)
- [ ] Virus Serum Toxin Act of 1913, amended 1985 (21 U.S. Code 151 – 159 et. seq.)
- [ ] Title 9, Code of Federal Regulations (Subchapter E, Parts 101 – 124), prior to 1997
- [ ] Title 9, Code of Federal Regulations (Subchapter E, Parts 101 – 124), 1998 or later
- [ ] Memorandum of Understanding Between the Animal and Plant Health Inspection Service, United States Department of Agriculture, and the Food and Drug Administration, Department of Health and Human Services (MOU # 225-82-7000), 1982
- [ ] Memorandum of Understanding Between the Animal and Plant Health Inspection Service, United States Department of Agriculture, and the Food and Drug Administration, Department of Health and Human Services (APHIS Agreement # 04-9100-0859-MU; FDA Serial # or MOU # 225-05-7000), 2013
- [ ] Office of Science and Technology Policy (OSTP) for the Coordinated Framework for Regulation of Biotechnology, 1986
- [ ] OSTP update for the Coordinated Framework for Regulation of Biotechnology, 1992
- [ ] OSTP update for the Coordinated Framework for Regulation of Biotechnology, 2017
- [ ] Center for Veterinary Biologics Notice No. 05-07 for Biologies for Reduction of Colonization and/or Shedding in Animals
- [ ] A written record of a previous request made by another person at the company where you worked
- [ ] One or more documents not identified above. Please describe the document(s), including any document names or numbers available to help identify them:

   [ ] No documents were used as resources.
Section A (10 questions)

A2. What PEOPLE did you consult for information regarding how to write or submit your FIRST jurisdiction request to USDA-CVB, before it was sent?

*Please do not mention people by name. Use only titles. Any proper names provided in your survey responses will be redacted during the review of your responses.*

**Choose ALL that apply.** For each person you select, choose the reason you consulted them.

- [ ] A colleague in the company where you worked
  - Primary Reason: --
- [ ] A person at another company, for example a contractor or consulting service
  - Primary Reason: --
- [ ] The Center for Veterinary Biologies – Policy, Evaluation and Licensing
  - Primary Reason: --
- [ ] A person not listed above (describe):
  - Reason: _______________________
- [ ] I did not consult any people

A3. To whom was your FIRST jurisdiction request sent to within the USDA-CVB?

- [ ] USDA-CVB Director
- [ ] USDA-CVB-Policy, Evaluation and Licensing, specifically:
  - [ ] The Reviewer assigned to the company
  - [ ] The Reviewer listed on the Memorandum of Understanding Between USDA and FDA
  - [ ] A Reviewer other than the above, due to previously working with that person
  - [ ] An individual other than the above, and explain the reason you chose them (if known):
    - _______________________
- [ ] USDA-CVB-Inspection and Compliance
A4. Please think about ONLY the FIRST jurisdiction request that you were involved in.

Which of the following items were included in the request?

Choose ALL that apply:

- The composition of the product
- A description of how the product was made or manufactured
- A description or classification that the product was a virus, serum, toxin or analogous product
- The proposed product label claims
- The product’s intended use to diagnose, cure, mitigate, treat or prevent disease in animals
- The species the product was to be administered to
- The planned route of administration
- A statement that the primary mechanism of action was immunological
- Experimental data supporting the primary mechanism of action was immunological
- A comparison of the proposed product to another product regulated by USDA-CVB
- Relevant scientific literature or reference citations
- A request that the jurisdiction be assigned to USDA-CVB
- Permission to share your information with the Food and Drug Administration – Center for Veterinary Medicine
- Additional items that were not identified above. Please describe:
Section A (10 questions)

Please read: One jurisdiction request to USDA-CVB begins with the initial request submitted to CVB and ends with the final decision for jurisdiction (or cancellation of the request for jurisdiction).

Please use this definition of one jurisdiction request to complete questions A5, A6 and A7 on this page.

A5. Using a four digit year (e.g. 1999 to 2000), what was the time period of your FIRST jurisdiction request, beginning with the initial request and ending with the final decision for jurisdiction (or cancellation of the request for jurisdiction)?

(Note: to protect anonymity, the specific years will not be summarized in the results of the thesis.)

Start: ___________________ to End: ___________________

A6. Identify approximately how many communications of each were required during your FIRST jurisdiction request, before an assignment of jurisdiction was made (or the request for jurisdiction was canceled).

If you did not use one of these forms of communications, select 0 for that item.

- Number of formal submissions, in writing: 0
- Number of informal, electronic mail communications: 0
- Number of scheduled meetings (teleconferences and meetings in person): 0
- Number of unscheduled telephone calls: 0

A7. After the initial request submitted to USDA-CVB, the USDA-CVB may have requested additional information in order to make a decision regarding jurisdiction. Please classify USDA-CVB’s requests for additional information.

Choose ALL that apply:

- [ ] There were no questions and the jurisdiction was assigned
- [ ] The composition of the product was required (or required further detail)
- [ ] A description of how the product was made was required (or required further detail)
- [ ] The proposed product label claims were required (or required further detail)
- [ ] Experimental data (or additional experimental data) was requested to support the primary mechanism of action was immunological
- [ ] Permission to share the information with the Food and Drug Administration – Center for Veterinary Medicine was requested
- [ ] Additional items were requested, that were not identified above. Please describe:

80
Section A (10 questions)

A8. During your FIRST jurisdiction request to USDA-CVB, was the jurisdiction assigned to USDA-CVB?

☐ Yes
☐ No – it was assigned to FDA
☐ No – it was assigned to EPA
☐ No – it was assigned to another agency
☐ No – a decision was never made (for example, if a project or request for jurisdiction was canceled)

A9. Based on your experience with your FIRST jurisdiction request to USDA-CVB, do you believe the resources available in the public domain are sufficient for a NEW regulator to make a request?

Please select the ONE answer which best fits your opinion.

☐ Yes, the resources in the public domain, such as the written acts, laws, regulations and guidance, are sufficient for a new regulator to make their first request
☐ No, a new regulator needs additional resources not available in the public domain in order to make a request

A10. Optional: In the space below, please share any further comments regarding your FIRST jurisdiction request to USDA-CVB that may assist a new regulator to make a request.

Thank you for completing this survey to describe your FIRST jurisdiction request to USDA-CVB.

If you have experience with 1 to 2 jurisdiction requests to USDA-CVB, then your survey is complete. Please save your survey and then email your completed survey to jhellstr@niga.edu.

If you have experience with 3 or more jurisdiction requests to USDA-CVB, then it is possible that your FIRST experience is different from your LAST or MOST RECENT experience in making a jurisdiction request to USDA-CVB. Please proceed to Section B of this survey (4 questions).
Section B (4 questions)

Please complete this section only if you have experience in at least 3 jurisdiction requests to USDA-CVB.

(If you do not have experience, skip to Section C. If you have experience in making 1 to 2 jurisdiction requests to USDA-CVB, then your survey was done by completing Section A and you should save then email your completed survey to jhellstr@uga.edu.)

B1. Please consider the LAST or MOST RECENT time you made a request for jurisdiction to USDA-CVB.

Please rank the importance of the following resources, based on your MOST RECENT knowledge and experience. If an item below is NOT important, then leave the ranking blank. If an item below IS important, then assign a 1 to the most important item, 2 to the second most important, and so on. Use each number only once.

The Virus Serum Toxin Act
The Code of Federal Regulations
The Memorandum of Understanding Between APHIS-USDA and FDA-DHHS
The OSTP Policy for the Coordinated Framework for Regulation of Biotechnology
Center for Veterinary Biologies Notice 05-07
Your previous experience in making jurisdiction requests to USDA-CVB
Consultation with other people in the company where you work
Consultation with other people in other companies, including contractors or consultants
Consultation with CVB-PEL
Other item not listed above (describe):
Section B (4 questions)

B2. Please identify which items should be included in a request for jurisdiction to USDA-CVB based on your MOST RECENT request for jurisdiction to USDA-CVB.

Choose ALL that apply.

☐ The composition of the product
☐ A description of how the product is made or manufactured
☐ A description or classification that the product is a virus, serum, toxin or analogous product
☐ The proposed product label claims
☐ The product’s intended use to diagnose, cure, mitigate, treat or prevent disease in animals
☐ The species the product is to be administered to
☐ The planned route of administration
☐ A statement that the primary mechanism of action is immunological
☐ Experimental data supporting the primary mechanism of action is immunological
☐ A comparison of the proposed product to another product regulated by USDA-CVB
☐ Relevant scientific literature or reference citations
☐ A request that the jurisdiction be assigned to USDA-CVB
☐ Permission to share your information with the Food and Drug Administration – Center for Veterinary Medicine
☐ Additional items that were not identified above. Please describe:

B3. Based on your experience overall, including your MOST RECENT jurisdiction request to USDA-CVB, do you believe the resources available in the public domain are sufficient for a NEW regulator to make a request?

Please select the ONE answer which best fits your opinion.

☐ Yes, the resources in the public domain, such as the written acts, laws, regulations and guidance, are sufficient for a new regulator to make their first request

☐ No, a new regulator needs additional resources not available in the public domain in order to make an effective request
B4. **Optional:** In the space below, please share any further comments regarding your OVERALL experiences in making jurisdiction requests to USDA-CVB that may assist a new regulator to make a request.

Thank you for sharing your knowledge and experiences in making jurisdiction requests to USDA-CVB. **Your survey is complete.** Please save your survey and then email your completed survey to jhellstr@uga.edu.
Section C (5 questions)

Please complete this section only if you do NOT have formal experience in making a jurisdiction request to USDA-CVB.

This may occur if you have not yet been involved in making a formal request to USDA-CVB, but you have knowledge or an opinion that you would like to share. Informal knowledge may include:

- Presentations, workshops or trainings you attended
- Your personal research into the requirements
- Previous conversations with people in industry or government
- Consulting resources described in the survey while completing the survey

C1. What resources would you use for information regarding how to write and submit your first jurisdiction request to USDA-CVB, before you submit it? Please select ALL that apply.

☐ Virus Serum Toxin Act of 1913, amended 1985 (21 U.S. Code 151 – 159 et. seq.)

☐ Title 9, Code of Federal Regulations (Subchapter E, Parts 101 – 124)

☐ Memorandum of Understanding Between the Animal and Plant Health Inspection Service, United States Department of Agriculture, and the Food and Drug Administration, Department of Health and Human Services (APHIS Agreement # 04-9100-0859-MU; FDA Serial # or MOU # 225-05-7000), 2013

☐ Update to the Coordinated Framework for the Regulation of Biotechnology, 2017

☐ Center for Veterinary Biologics Notice No. 05-07 for Biologics for Reduction of Colonization and/or Shedding in Animals

☐ One or more documents not identified above. Please describe the document(s), including any document names or numbers available:
Section C (5 questions)

C2: What PEOPLE would you consult for information regarding how to write or submit your FIRST jurisdiction request to USDA-CVB, before it is sent?

Please do not mention people by name. Use only titles. Any proper names provided in your survey responses will be redacted during the review of your responses.

Choose ALL that apply. For each person you select, choose the reason you would consult them.

☐ A colleague in the company where you work
Primary Reason:  

☐ A person at another company, for example a contractor or consulting service
Primary Reason:  

☐ The Center for Veterinary Biologies – Policy, Evaluation and Licensing
Primary Reason:  

☐ A person not listed above (describe):
Reason:  

☐ I would not consult any people

C3: What would you include in your request? Choose ALL that apply.

☐ The composition of the product
☐ A description of how the product is made or manufactured
☐ A description or classification that the product is a virus, serum, toxin or analogous product
☐ The proposed product label claims
☐ The product’s intended use to diagnose, cure, mitigate, treat or prevent disease in animals
☐ The species the product is to be administered to
☐ The planned route of administration
☐ A statement that the primary mechanism of action is immunological
☐ Experimental data supporting the primary mechanism of action is immunological
☐ A comparison of the proposed product to another product regulated by USDA-CVB
☐ Relevant scientific literature or reference citations
☐ A request that the jurisdiction be assigned to USDA-CVB
☐ Permission to share the information with the Food and Drug Administration – Center for Veterinary Medicine
☐ Additional items that were not identified above. Please describe:
Section C (5 questions)

C4: To whom would you submit your jurisdiction request to within USDA-CVB?

☐ USDA-CVB Director
☐ USDA-CVB-Policy, Evaluation and Licensing, specifically:
   ☐ The Reviewer assigned to the company
   ☐ The Reviewer listed on the Memorandum of Understanding Between USDA and FDA
   ☐ A Reviewer other than the above, due to previously working with that person
   ☐ An individual other than the above, and explain the reason you chose them (if known):

☐ USDA-CVB-Inspection and Compliance
☐ Not sure, additional comments (if any):

C5. Based on your knowledge, do you believe the resources available in the public domain are sufficient for you to make an effective request to USDA-CVB for jurisdiction of a new biotechnology product? Please select the ONE answer which best fits your opinion.

☐ Yes, the resources in the public domain, such as the written acts, laws, regulations and guidance, are sufficient for me to make my first request
☐ No, I would need to supplement the resources in the public domain with additional information in order to make an effective request
☐ Not sure, additional comments (if any):

Thank you for describing how you might prepare or submit a jurisdiction request to USDA-CVB. Your survey is complete. Please save your survey and then email your completed survey to jhellers@uga.edu.