THE USE OF HUMAN DRUGS OFF-LABEL IN ANIMAL HEALTH: THE VALUE OF MAKING AN ANIMAL APPROVED DRUG PRODUCT AND THE PUBLIC'S OPINION

by

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(Under the Direction of David Mullis)

ABSTRACT

Animal health may significantly affect human health. There is a shortage of drugs approved for animal use; therefore veterinarians use some drugs in an off-label manner to treat patients. FDA and USDA approved drugs must go through extensive research and development to provide evidence of safety and effectiveness before they may be sold. With veterinarians using human drug products off-label, is it cost effective for animal health companies to develop an animal derivative? Will pet owners be willing to possibly pay more for a product that is approved for use specifically for their pet? A literature review, survey and interviews were conducted to answer these questions which found that the costs could be worth the investment, if the drug was made with a unique aspect for animals and marketed as such. In addition, more than half of respondents to the survey and interviews were willing to pay more for an animal approved drug product.

Index Words: Veterinary Health, Animal Health, Food and Drug Administration (FDA), Off-label drug use, Extra Label Drug Use

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DEDICATION

I dedicate this thesis to my family for fully supporting me in my goals to attain higher education.

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CHAPTER ONE: INTRODUCTION

Purpose of the Study

There is limited literature or information available about the use of human drugs off-label in the treatment of animals with regards to costs and revenues that the sales bring to human drug companies. Most literature available today discussing off-label use of human drugs in animals looks at the impact of the drug use for a specific case study to provide veterinarians information that they can use to assess the possibility of using the same methodology of treatment for their animal patients. There is also limited information published about the public's opinion on consumers' willingness to potentially spend more on their pets when it comes to veterinary care. It is not known if pet owners prefer the option of using human drug products off-label on their pets, or pay more for a drug approved or licensed by FDA and/or USDA, respectively based on clinical studies. What is known is that making human drug products with a simple administration dosage form is in demand by veterinarians to maximize owner compliance, and make providing medications to pets easier for the pet owner.[1]

The purpose of this study was to collect and systematically analyze the information from a sample of pet owners and animal health professionals about off-label use of human drugs in animals in regards their economic benefit use versus an approved use. Human drugs are used off-label even when they are prescribed for humans, and the practice is common in specialties such as pediatrics, pain medicine and palliative care, with up to one quarter of all prescriptions falling into this category.[2] Off-label use of products by veterinarians is not regulated by the FDA, as it falls under the practice of medicine. The FDA only regulates products in relation to their

approved claims. Off-label use could be classified as misbranded if the drugs are marketed for the off-label claim.

The purpose of this qualitative and quantitative study was to determine if it is worth the time and cost to develop an animal pharmaceutical drug when an approved human drug is currently on the market being prescribed off-label by veterinarians. The scope of this study focused only on human and animal drug products regulated by the Food and Drug Administration (FDA) and excludes topical animal pesticide products and animal biological products. Even though antibiotic products are the most widely used off-label category, they were not covered in this study due to ongoing issues such as antibiotic drug resistance. The concern of antibiotics is in the potential for resistant strains to develop within animals, subsequently making products less responsive for human health.[3]

This study reviewed the average costs and times for human and animal pharmaceutical drug products to receive approval in the United States, as well as personal opinions on animal health. Animal drugs appear to be more expensive than the brand name human drug counterpart, which could be contributed to the insurance coverage provided for human medications. Another contributing factor to costs is that the generic form of the human counterpart can be more cost effective than the brand name veterinary drug product. For example, the human drug Prozac®, without insurance reimbursement can cost $5,000 for a 30 count of the 10mg tablet while the generic fluoxetine costs $11 at the local pharmacy for the same dosage strength and count.[4] The veterinary drug counterpart, Reconcile™ which is no longer available, used to be listed for $51.50 for 8mg 30 count bottle.[5] The two main questions that were studied were:

1. Is it worth the time and money to develop an animal drug from an already approved human drug being used off-label in animals?

2. Will pet owners be willing to pay more for an animal approved drug when a human approved drug product is available?

These questions were evaluated by looking at the costs and time of bringing an animal drug to market, the potential revenues that a human drug is accruing when used in the animal health field, as well as a survey and interviews for public opinions.

The population targeted for the study encompassed a sample of randomized adults, age 18 or older, living within the US, owning pets and/or working within the human or animal health industry. The randomization of participants in the survey was established through social media account groups which helped to reduce potential biased results through contacting individuals that the researcher knew personally. However, the use of social media potentially could be considered a source of bias by only providing the survey through this avenue. Interviews were randomized through e-mails sent to a random group of addresses acquired through several years of undergraduate school in the area of study of biology, graduate school in the area of study of pharmaceuticals, previous and current work contacts comprising from the service industry to the veterinary industry, and other acquaintances. The e-mail requested participation in the study for a personal interview of their opinions on the animal health industry to provide more details on opinions that the survey could not fully cover.

This thesis intended to provide information on the potential revenue a pharmaceutical company can make by registering a product with an animal label when the human labeled product is already used off-label for animal health. It also intended to provide pet owners' opinions on their willingness to potentially pay higher costs to purchase these animal labeled products.

Expected Results

The outcomes of this research had the potential to vary greatly. Prior to conducting the research, it was hypothesized that the revenue to be gained by an animal pharmaceutical company for bringing an animal drug product to market will be worth the costs of research, development and approval even when there already is a human drug product available that is currently being used off-label for animals. In addition to the value of a new product for the animal health industry, it was hypothesized that the majority of the population will prefer to use drugs that are approved for use in the target animal species versus the off-labeled use of human drug products, even if it means potentially higher costs. The public's opinion could possibly be influenced by several factors related to their level of education, number of pets they own, and their age. Marketing research has shown that a person's social class in relation to their occupation, education, income, age and number of dependents can influence what a person is willing to spend their money on.[6]

While these hypotheses would be the ideal situation for both the animal patients themselves and the animal health industry, the results could be different. The alternative to the proposed hypotheses could be that the revenues to be gained by the animal health company may not outweigh the cost and time to research and develop a product with an animal label when there is a human product available to use. The general population may not agree with the potential higher cost of the animal approved drug when there is a human drug available to use at a reduced price.

In order to evaluate the research questions, the data collected within the survey were reviewed and the hypotheses tested. The influences to whether the participant would be willing to spend more (age, education and number of pets owned) was tested using Fisher's Exact test

through Statistical Analysis System (SAS) program software to determine statistical significance in these variables from the responses to the survey. One on one interviews were conducted with similar questions to the survey in an attempt to provide more depth and support the answers received in the survey.

Potential Benefits

The animal health industry has grown steadily over the years, but there remains many human drugs that are prescribed off-label for animals because there is not an animal equivalent drug product available. By conducting this review, the results of this study may help contribute to furthering our understanding of the animal health industry, not only for the costs and time benefits for the industry itself, but also for the customers and animals that help sustain the industry.

If the results of this study show that it is worth the cost and time to bring a product to market with an animal approved label, it may encourage the animal health industry to invest in the approval of new animal drugs that are currently human drug products used off-label. If the results also show that the general public is willing to spend more on these animal approved products, it could also help justify the costs for the animal health industry to invest more into bringing these products to market. This study may also help veterinarians understand client's true opinions on what they are willing to do to provide care for their pets in terms of the money they are willing to pay, as well as their general level of understanding of the animal health industry and how it relates to the costs associated with animal drug products.

If more products are available for veterinarians to prescribe to pets that have the animal approved label, veterinarians will be able to provide a higher quality of care through medication

that has documented proof of the true risks and potential benefits of the product in the targeted species. This information can be used to communicate more effectively with clients when choosing the best option in treating their pets.

However, if the costs and time associated with bringing a new animal drug to market that is already approved in the human health industry is not worth the expenditure, then this study will help highlight the need to understand why this is the case, and how the animal health industry and the FDA can work together to make this pursuit worth the effort. If the results of this study show that pet owners are not willing to pay the additional costs, it will highlight the need to understand why this is the case. The rationale behind this could be related to their economic status, how many pets they are taking care of, animal insurance, lack of understanding as to why the cost is more, or lack of understanding as to why it is important to have their animal species on the label. Understanding this may encourage the use of education either from the animal health industry itself, or directly from veterinarians so that pet owners understand the importance of having products that are approved specifically for their pet's species.

Education and awareness should be encouraged if both of these aspects reveal that it is not worth bringing an animal approved drug product to market, not provide an excuse to avoid developing animal health products specifically proven safe and effective for the target animal species. Regardless of the outcome of the study, it will add to the general knowledge of the animal health industry. This knowledge will benefit not only the animal patients, but also the general public health as animal health is an integral part of our everyday lives.

CHAPTER TWO: BACKGROUND

Regulatory Agencies in the US for Animal and Human Health

Animal drugs are regulated by three different governmental agencies in the United States, the Environmental Protection Agency (EPA), the United States Department of Agriculture (USDA), and the Food and Drug Administration (FDA). Which agency regulates the animal drug depends on the mechanism of action and the intended use. Human drugs are regulated only by the FDA. The center within the FDA that regulates human drug products is determined by the product's intended use and mechanism of action as well. Each agency or center within the FDA receives its authority through different Acts or laws developed by Congress.

The EPA is responsible for ensuring that all pesticides sold in the US "do not cause unreasonable risks when they are used according to the instructions on the label"[7]. Their mission is to "protect human health and the environment"[7]. The EPA studies environmental issues, educates the public about the environment, and regulates pesticides. This agency regulates animal pesticide products, as well as human pesticide products. The EPA reviews and registers non-systemically active pesticide products for animals typically known as flea and tick products. Some of the flea and tick products are systemic and are therefore not regulated by the EPA; they are regulated by the FDA. In order to distinguish which authority has the jurisdiction over a particular product, the EPA and the FDA have a memorandum of understanding for pesticide products based on their mechanism of action. The non-systemically active products regulated by the EPA for animals include shampoos, collars, dust or powders, sprays and spot-on products. The human products the EPA regulates include mosquito and tick repellants.

The EPA is given its authority under the Toxic Substances Control Act (TOSCA) of 1976 which allows the EPA to require reporting, record-keeping, testing requirements and restrictions relating to chemical substances.[8] In addition to the TOSCA Act, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides the EPA with control of pesticide distribution, sale and use.[7] The EPA is required to set pesticide tolerances for all pesticides used in or on food under the Federal Food, Drug and Cosmetic Act. FIFRA and the Federal Food, Drug and Cosmetic Act were amended by the Food Quality Protection Act (FQPA) of 1996, requiring stricter safety standards, and complete reassessment of all existing pesticide tolerances.[9] The Pesticide Registration Improvement Act of 2003 (PRIA) helped create more predictable evaluation process for pesticide decisions and enable the collection of fees with specific decision review periods.[10]

The second agency, the USDA, helps support the agricultural economy, protects and conserves natural resources and helps to provide a safe food supply for the United States. The USDA is made of several agencies and offices in order to carry out their mission. The Animal and Plant Health Inspection Service (APHIS) is an office within the USDA which is responsible for managing agriculture from pests and disease and also manages wildlife. This office is given its authority under the Animal Welfare Act.

The Center for Veterinary Biologics (CVB), within APHIS, is responsible for the review and approval of biological products for animals under the Virus-Serum-Toxin Act of 1913. This Act "forbids the preparation, sale, barter, exchange or shipment of worthless, contaminated, dangerous or harmful animal biologicals in interstate commerce."[11] The 1913 Act was amended by the 1985 Food Security Act, "to ensure that all veterinary biologics produced in, or imported into the US are not worthless, contaminated, dangerous, or harmful."[11] Animal biologic products

include vaccines, bacterins, antisera, diagnostic kits and other products that are biologic in origin that generally work through a type of immunological process.[12] The Title 9 Code of Federal Regulations Part 101-122 provide the laws in which a manufacturer must follow in order to manufacture and sell an animal biologic. Similar to the EPA, the USDA and FDA at some points overlap on their jurisdiction of animal products and therefore follow a Memorandum of Understanding. In this Memorandum, the agency responsible for the product will be dependent on what the drug's primary mode of action is. Generally, if the product works through an immunological response, it will be regulated by the USDA.[12]

The third agency, the FDA, is responsible for both animal pharmaceuticals as well as all human pharmaceuticals. It is responsible for regulating food, dietary supplements, drugs, medical devices, cosmetics, biologics, biological products, and veterinary drugs. The FDA has five main centers, the Center for Veterinary Medicine (CVM), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and the Center for Food Safety and Applied Nutrition (CFSAN).[13]

CVM is responsible for the review and approval of animal pharmaceutical drugs, and is responsible for monitoring veterinary medical devices. It ensures that animal drugs are safe and effective, and monitors the products in the market through post market surveillance.[14] The FDA receives its authority from the Food, Drug and Cosmetic Act as well as several other acts and amendments that will be discussed later in the history of animal and human health. For the purpose of this study, only animal pharmaceutical drug products approved by the FDA will be reviewed as this is the only agency that approves both human and animal drug products. Since animal medical devices are not subject to a full clearance process through CVM, comparable to

the human medical devices clearance through CDRH, they will not be in scope of this study either.

CDER is responsible for the approval and monitoring of human drugs, and certain therapeutic biological products. The center regulates over-the-counter and prescription drugs, as well as fluoride toothpaste, antiperspirants, dandruff shampoos and sunscreen.[15] For the purpose of this study, only human pharmaceuticals approved through CDER will be considered. Medical devices, biologics and combination products for humans that are reviewed and approved or cleared through CBER or CDRH respectively will not be included.

History of Animal and Human Health

Before the regulatory agencies EPA, USDA and FDA that we know today, products were sold on the market with no proof of efficacy or safety. These products advertised a wide variety of claims like the ability to rid worms from animals which were made with nicotine. Farmers had home remedies for their animals, but there was no information or proof that any of these products actually worked, let alone were safe. The issues with efficacy and safety of health care products not only affected animal health care products; it also affected human health care products.

Starting in 1906, with the passage of the Pure Food and Drugs Act, food and drugs were regulated for "man or other animals". This was the first act that provided a legal definition of 'adulterated' and 'misbranded' and allowed the Bureau of Chemistry (precursor to the FDA) to seize adulterated or misbranded products that were in interstate commerce and adopted the drug standards published in the US Pharmacopeia and National Formulary (USP-NF).[16] The Pure

Food and Drugs Act started the evolution with the concept of drug purity. From this point forward, the history of animal health closely followed the history of human drugs.[17] As issues occurred in the human health sector, new Acts were passed to improve both the human and animal health industries.

In 1938, the Federal Food, Drug and Cosmetic Act was passed, which addressed the concept that drugs must be safe. This Act was triggered by the incident in human health with the drug Sulfanilamide. The drug had no safety information (no animal drug testing was performed[18]) which contained diethylene glycol (antifreeze), and killed many. Almost 30 years later, the Kefauver-Harris Drug Amendments were passed to address the concept that drugs must be effective, in addition to being safe. Like the Federal Food, Drug and Cosmetic Act, the Kefauver-Harris Drug Amendments were needed in response to a tragedy where children were deformed when their mothers took thalidomide while pregnant. This drug was already approved in Europe, and had been submitted for approval to the FDA. However, the FDA refused to approve the product due to its scrutiny of the lack of safety information available.[19]

As more acts were passed in congress to advance the review and approval of human drugs, they sometimes created a burden on the ability for animal pharmaceutical manufactures to obtain an approval for an animal drug. According to the American Veterinary Medical Association (AVMA) one of the main reasons why so few animal drugs exist is due to the high cost and length of time it takes to receive FDA approval, and the fact that the profit margin is not as high as human drug products.[20]

Recently, several key acts helped improve the review and approval of animal drug products. The Animal Medicinal Drug Use Clarification Act of 1994 made extra labeled drug use (ELDU), also known as off-labeled use, an FDA-regulated veterinary activity, providing

veterinarians with a valid veterinary/client/patient relationship the flexibility to prescribe products off-label of an approved animal and/or human drug when the health of an animal is "threatened, when suffering, or if death may result from failure to treat the animal".[20] The term off-label is defined when a physician or veterinarian prescribes a drug in a way that is not specifically indicated on the label. This can include a different dosing size, different ailment than what the drug is labeled to treat, a different treatment regimen, as well as a different species that is not explicitly stated on the label.

Before this Act was passed, it was illegal for veterinarians to provide human drugs off-label to animals because the FD&C Act deemed that a drug was considered unsafe unless it was subject to the FDA's approval process for exactly what was on the label (per species, the disease, dose, route of administration).[20] While this act made off-label prescribing legal for veterinarians to provide more options for pet owners, it was not intended to slow down the animal health industry by decreasing the urgency to produce these products with a label specifically tested and approved for use in the targeted animal species.

In 1990, the Animal Drug Availability Act (ADAA) provided CVM with the flexibility to streamline requirements for animal drugs and medicated feeds. Less than ten years later, following the establishment of the Prescription Drug User Fee Act (PDUFA) enacted in 1992 for human pharmaceuticals, the Animal Drug User Fee Act (ADUFA) was passed to allow FDA to collect fees from drug sponsors. These fees were established to enable the FDA to expedite and improve the review of applications for animal drugs. It provides the user fees and also a review timeline in which the FDA will provide its completed review response for a submission.[17] The review timeline helps manufactures of animal drugs anticipate approval dates. By having a timeline to reference, the animal health industry can estimate targeted launch dates and ensure

supply chains are established to deliver the product to customers as soon as possible once approval is received from the FDA.

Another act designed to help the animal health industry was the Minor Use and Minor Species (MUMS) Animal Health Act in 2004. This Act was passed to help medication availability for minor animal species (all species other than human or animal species not defined as major, example zoo animals), and for diseases that are not very common in major species (horses, dogs, cats cattle, pigs, turkeys and chickens). This Act was important because "before passage… companies could rarely afford to bring to market drugs for minor species because the markets were too small to generate an adequate financial return".[17] This provided the animal health industry with the ability to have a conditional approval of a product. The conditional approval allowed sponsors to make the drug available after it provided proof that the drug was safe, and before collecting all effectiveness data as long as there was a reasonable expectation of effectiveness. This act was also designed to help sponsors apply for grants with the "designated" products and could receive seven years of marketing exclusivity. Sponsors are also able to apply to waive user fees, and the Compliance Policy Guide for extra-label use of Medicated Feeds for Minor Species directs FDA field officers to have a low enforcement priority. This low enforcement policy meant that the FDA would be less likely to take action against off-labeled use of a feed in other species that are not on the label.[21]

Even with all of the efforts to improve animal health drug product availability, there is still the need to use human products off-label because there is not an equivalent product available with the label for animal species. This is a gap in animal health care that needs to be addressed. The issue needs to be discussed more between industry, government and the general public to determine what can be done to close that gap. By having products available with testing and

documented evidence of safety and effectiveness, veterinarians can provide better treatment options for their patients.

Human Pharmaceuticals

Prior to using an unapproved drug in humans, a drug must go through pre-clinical studies, which includes animal testing. Once the drug is determined to be reasonably safe, the manufacture must submit and receive an approval of an Investigational New Drug Application (IND) before it can begin testing in humans. Once an IND is approved by the FDA, the drug will go through three phases of human clinical trials, four if including the post approval phase. The first phase is used on a small sample of individuals, around 20 to 80, that are typically healthy to assess the safety and toxicity of the product. The second phase is assessed on a larger sample of individuals with the disease, usually around 100 to 300 individuals. This phase is used to determine the drug's effectiveness and establish the dosages. The third phase uses an even larger sample of individuals with the disease, around 1,000 to 3,000. It is used to assess the effects of the drug to monitor for side effects and reinforce the drug's effectiveness and safety.[22]

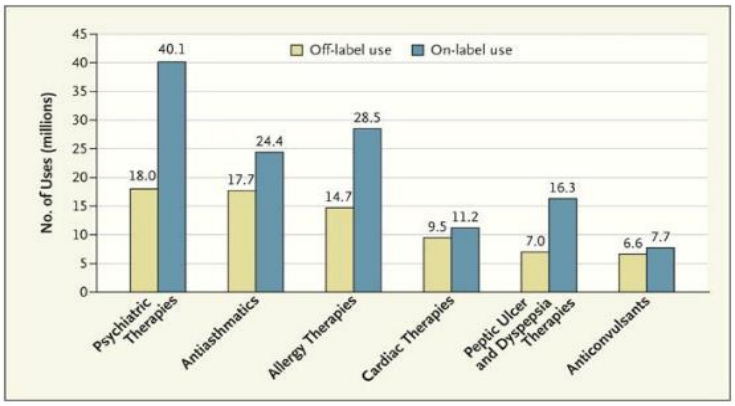
Following the successful third phase clinical trial, the manufacture submits a New Drug Application (NDA) to the FDA. If successful, the FDA will approve the product and the product can be sold on the market.[23] For a molecule to make it from the laboratory through clinical testing and onto a pharmacy shelf, it takes an average of 12 years, and it costs around 350 million dollars.[24]

The top human pharmaceutical companies based in the United States include Pfizer, Eli Lilly, Merck, and Abbott Laboratories. These pharmaceutical companies have impressive

revenues and market shares. For example, in 2014 Pfizer held 203.93 billion in market capitalization and 172.1 billion worth assets.[25]

Some of these companies have an animal health sector which also supports the business, but is not the area where they generate the most revenue. The high revenue comes from the human drugs that they sell where the margins are significant. Some manufactures are choosing to break off their animal health sectors because of this, while other manufactures without an animal health entity want to gain the extra revenues. For example, in 2012, Pfizer announced that its animal health sector would become a standalone company Zoetis. The opposite is true for Sanofi, a human pharmaceutical company which gained an animal health sector, Merial.[25]

Human drugs must also show proof of safety and efficacy, but only for one species. The human drug may have limited label claims, and may be used off-label for other indications not specifically on the label or with evidence to support its efficacy. The human drug may receive new indications on the label through supplemental regulatory applications; however, due to generics and the wide use of the product already in the market for the off-label indication, it is not always cost effective for the manufactures to conduct clinical testing to receive the label claim. For example, a report showed that for the 3 leading drugs in 15 leading drug classes, off-label use accounted for approximately 21% of the perscriptions.[26]



Estimated Numbers of Prescriptions for On-Label and Off-Label Uses of Medications in Various Functional Classes, 2001.

Numbers were estimated on the basis of the National Disease and Therapeutic Index, a survey conducted by IMS Health. Data are from Radley et al.[2]

FIGURE 1: Estimated Numbers of Prescriptions for On-Label and Off-Label Uses of Medications [26]

This figure shows that even with the extensive research conducted for human health, there are still un-met needs for approved new indications.

Animal Pharmaceuticals

An animal drug may not be sold into interstate commerce unless it is approved by the FDA through a New Animal Drug Application (NADA). For a manufacture to start shipping investigational drugs to studies for the targeted animal species there must be some pre-clinical work completed and the manufacture must submit an Investigational New Animal Drug Application (INAD). Once the INAD is approved and data and information is collected, the sponsor must then submit the NADA to provide documented evidence that the drug product is both safe and effective. There are several types of studies, but the studies are not laid out in the three clinical trial phases as seen in human health. The drug is considered to be safe if "adequate tests by all methods reasonably applicable show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling".[27]

The categories for safety testing include target animal safety, human food safety, and environmental safety. For the drug to be considered effective, the manufacture must provide evidence consisting of one or more adequate and well controlled investigations into the target species, laboratory animals, field studies, bioequivalence studies and in vitro studies. These studies for efficacy should "fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling."[27] There are approximately 300 drugs currently approved by the FDA for use in companion animals. Some consist of the same active ingredient in the human drug counterpart, and must still go through the full approval process through CVM.[13]

On average only 1 in about 7,500 compounds succeed in a successful and marketable product approval in animal health.[28] The time that it takes to bring a concept to an approved product for companion animals takes a large investment in research and development, usually around five to seven years. It can take an additional two and a half to four years to receive approval from the FDA to market the finished product in the United States for an animal drug. This means approximately 7-10 total years. In addition to a substantial amount of time, the potential costs can reach up to 200 million dollars to develop a major new animal drug.[20] With the time consumed with development and approval, the amount of time left on the drug's patent is limited. The manufacture has the ability to request patent term extensions based on the amount of time the drug spent in the review process in the FDA. Patents are important to the manufactures to prevent generics on the market to allow the originator to make profits to level out the investment they had to make to bring the product to market. In order for the manufacturer to continue to invest in making new innovative products, it needs to make a profit.

Based on the referenced data for costs and time associated with human and animal drugs, the cost for an animal drug is approximately 150 million dollars less than the cost of bringing a human drug product to the market, and only takes a few years less time than a human drug approval. The cost of bringing an animal product to market has on average increased over the years just as in human health. Over a 5 year period from 2006 to 2011, the average cost increase for a new animal drug was about 25%. Even with the heavy price tag and extensive time, the animal health industry worldwide is worth 23.0 billion dollars and has a nominal growth of +2%.[29]

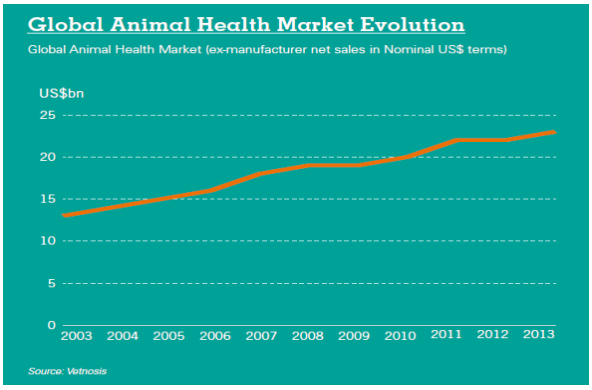


FIGURE 2: Global Animal Health Market Evolution [29]

The top ten animal health companies include Bayer Animal Health, Boehringer Ingelheim, Elanco, Merck Animal Health, Merial, Novartis (now integrated into Elanco in 2014), Verbac Animal Health, and Zoetis.[30] The top earning company, Zoetis, made 4.56 billion dollars in revenue for the year 2013. Compare this to the highest earning human health company, Pfizer, at 51.6 billion dollars in 2013.[31] The human health care company made around ten times as much profit as their spin off animal health sector Zoetis. Companion animals and equines contribute to 43% and 10% of the animal health business.[32]

The actual percent of profit human pharmaceuticals make for their products when used off-label in animal health is not precisely known. There was a report in 2011, that Americans

spent nearly $7 billion on psychiatric human pills for their pets, which was up 35% in four years.[66] If the rate of growth continued at 35% since 2011, it could mean nearly $9.5 billion will be spent towards psychiatric pills in 2015. Since psychiatric medicine is not the only type of medication used off-label for animals, the number of actual spending on human products used off-label in animals could potentially be higher.

Importance of Animal Health for Humans

Humans rely on animals in many aspects of their lives. From the food we consume to the pets we take care of, the health of animals is crucial to the health of humans. We depend on animals on a daily basis as resources such as food, income, companionship and aids for disabilities. A majority of pet owners have more than one pet; households with children are more likely to have pets, while single persons are less likely to own pets. Some studies have reported that pet-owning pre-adolescents score higher on measures of self-esteem and autonomy.[34] Approximately two thirds of the diseases known to affect humans can be transferred between humans and animals (zoonotic diseases), and three out of four emerging diseases affecting humans have come from animals.[35] With the close contact humans have on a daily basis, and the ability for diseases to transfer from animal to human, it is important to keep animals healthy. There are billions of production animals such as poultry, cattle, sheep, goats and pigs, and there are several million companion animals such as dogs, cats and horses. To keep all of these animals healthy, their medications need to be widely available, appropriate for the disease they intend to treat, and safe and effective for each species.

In addition, pet owners have grown more concerned with providing comfort to their pets while they are suffering, and extending their lives. Pet owners consider themselves as "parents" and treat their animals as if they are part of the family. Some are even willing to spend money on expensive surgeries and medicines to provide for their pets. With this mentality towards animals, the animal health industry should continue to grow as the demand for better health for animals increases.

Advantages and Disadvantages for Off-label Use

There are advantages and disadvantages to off-label drug use whether the product is being used in humans or in animals. Drugs are tested to determine if they are safe and effective for use, and without the testing, there would be no documentation of their benefits and their associated risks. When using drugs off-label these aspects are not explicitly known and the outcome is imperative for the patient receiving the treatment. Analyzing the advantages versus the disadvantages to off-labeled drug use can help the public understand the risks associated with the use of these products in their animals when using a human drug off-label as well as help physicians and veterinarians remain informed on best prescribing practices.

Prior to a drug being tested in humans during human clinical trials, the drugs are tested in several animal species or models. If the drug effects in animals provide evidence of reasonable safety, these tests are typically used to justify the use in humans. Claude Bernard, known as the father of physiology, states that "experiments on animals are entirely conclusive for the toxicology and hygiene of man. The effects of these substances are the same on man as on animals, save the differences in degree."[18] The efficacy and safety for a specific companion animal species such as dogs, cats and horses may not be known or tested during the animal

testing for a human drug, as the species used is not an exhaustive list. There are other scientifically based animal models that better predict a drug's profile in man such as the dog or pig while others do not due to anatomical and physiological differences. There are examples when a diabetes medicine was tested in dogs before use in humans, but was not formally approved for that use in dogs.[26] If the information is available, animal health companies could use these studies to develop a faster path for making a drug label for the diabetes drug with an approved label claim for dogs.

However, there are differences between humans and animals that make certain products more or less tolerable. Take a food for example: chocolate. It is a treat for a human, but is toxic for dogs. This same concept is true for some drugs. What needs to be taken into account when attempting to make an animal label for a human drug include how the drug is administered, the dosage and metabolic breakdown of the drug itself.

Minor differences in the formulation of a drug may produce alterations in the pharmacokinetics and biological availability in the animal species compared to humans.[20] The digestive system itself is generally shorter in companion animals such as dogs and cats than their human care givers. The time it takes for a drug to travel through the digestive system is approximately half the time for humans, which is about 24 hours.[36] There are several examples of drugs that were originally approved as human drugs that have subsequently been formulated, either by mode of administration or changes in dosage amounts, to work more effectively for animals.

Examples of human drugs that are used quite frequently include behavioral drugs also known as antidepressants like Prozac (fluoxetine), which there was an equivalent product for animals called Reconcile (fluoxetine) by Elanco. Antidepressants are used in animals for

obsessive compulsive behaviors such as excessive grooming, separation anxiety, inappropriate urination, and aggression.[34] These products have the same active ingredient fluoxetine; however, the difference between Prozac and Reconcile is the administration form and the dosing. Prozac is provided in tablets at 10, 20 and 40 mg while Reconcile, which is no longer being produced for use in the US, was available as 8, 16, 32 and 64 mg chewable tablets.[5]

There are anti-inflammatories like Rimadyl® (carprofen), a product for dogs by Zoetis, which is comparable to Advil® (ibuprofen) for humans. Carprofen has a higher selectivity for COX-2 (129-fold) over COX-1 but is considered a weak COX inhibitor. It is believed that the COX-2 is active in damaged or inflamed tissues, while COX-1 is expressed in almost all tissues which may lead to undesired adverse effects. By having selectivity for COX-2, this may reduce the possible adverse effects as seen when COX-1 is also inhibited. Between dogs, cats and horses, the selectivity for COX-2 inhibition varies. Enteric-coated products (have a polymer barrier to protect against high pH) used in human medicine are not recommended for dogs because gastric retention may lead to erratic plasma exposure.[37] Firocoxib is another NSAID used in animal health that is in the coxib class of NSAIDs. Firocoxib is even more selective towards COX-2 (384 fold) than carprofen. Another coxib-class NSAID, robenacoxib, is structurally related to the human drugs diclofenac and luminracoxib and is approved in the US for cats.[37]

Some drugs that have already been adapted for veterinary use include ramipril, enalapril and benazepril which are angiotensin-converting enzyme (ACE) inhibitors commonly used in heart failure management in dogs.[34] There are some animal drug products in which the main chemical compound is from the same class of the comparable human drug product. An example of this is the tyrosine kinase inhibitors Gleevec® (imatinib) for humans by Novartis and

Palladia™ (toceranib) for dogs by Zoetis which are used as cancer treatments.[38] Toceranib was evaluated in canine mast cell tumors (MCT). The adverse events noted in dogs treated with toceranib were similar to other tyrosine kinase inhibitors in humans.[39] The following Table 1 provides a list of agents that are approved in both the human and companion animal health fields.

TABLE 1: Examples of Agents Approved for Use in Humans and Companion Animal Health[1]

	Examples[1]
Agents approved for use in human and companion animal health	ACE inhibitors—enalapril, benazepril, ramipril Antiemetics—domperidone Antifungals—nystatin, azoles (e.g., clotrimazole, miconazole), posaconazole Antiprotozoal—miltefosine Corticosteroids—betamethasone valerate, hydrocortisone aceponate, mometasone furoate Diuretics—furosemide, spironolactone Gastric acid inhibitors—cimetidine, omeprazole Hormones—estriol, thyroxine Intravenous anesthetics—propofol Nonsteroidal anti-inflammatory drugs—meloxicam Macrocyclic lactones—ivermectin Mercaptoimidazoles—thiamazole, carbimazole Phosphodiesterase inhibitors—pimobendan a Receptor tyrosine kinase inhibitors—masitinib

In addition to the level between human and animal, there is also another level even between animal species such as dogs and cats, as well as between breeds of species such as the collie dog breed. There are differences in the gastric intestinal pH between species which can have an effect on how drugs are absorbed in the body.[36] Some medications can be harmful if used off-label for different species. Examples of this include morphine, which a dose that is okay for a small dog is unpredictable in cats and may cause apprehension, excitability, drooling, convulsion and death. The enzyme that helps metabolize morphine is deficient in cats, which may cause these side effects.[34] Collies have sensitivities to certain drugs, in particular

ivermectin. Collies have a recessive mutation mdr1-1Δ which is a genetic defect in the mechanism that prevents drugs from building up in the brain. This mutation has been found in low frequencies in Australian Shepherds, Shetland Sheepdogs, Old English Sheepdogs, McNabs, Long-haired Whippets and Silken Windhounds.[40]

Currently there are not enough drugs approved for use in animals to meet every animal's needs. There is a need to increase the availability of drugs that will improve care for animals. Improving characteristics such as the method of administration of a drug into an orally administrated drug would make it easier for veterinarians and pet owners to provide to their animals and remain compliant with the administration regimens. This transition of using currently approved human drugs to develop animal drugs is increasing, and can be seen in several animal health companies. According to Animal Pharm-World Animal Health and Nutrition News, amlodipine (Norvasc, Pfizer) and nifedipine are calcium-channel blockers that are likely to be developed into animal drugs. Other drugs that may be entering the animal drug market could include fosinopril, lisinopril, and quinapril.[41]

There are several companies such as Kindred BioScience and Aratana that are publically providing information on drugs in the pipeline that are being modified from approved human drugs, or tested to receive the additional label claim for use in targeted animal species. Aratana has conditional approval for two antibodies to treat lymphoma in dogs which have the same mechanisms of action as human drugs Rituxan® and Campath®.[42]

Some of the advantages of using drugs off-label include unforeseen drug discovery, like the case of the human drug Viagra®. This drug was originally tested as a heart medication, but during testing showed a side effect that was encouraging for impotency.[43] It also permits innovation in clinical practice. For drugs that do not have the approved label for specific

indications, it opens up the ability for patients and physicians to have earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence that may be provided through other physician testimonials, or other scientific articles.[26]

On the other hand, the disadvantages include the fact that it can undercut expectations that drug safety and efficacy have been fully evaluated. Also, when newer and more expensive drugs are used off-label, it increases health care costs, and undermines the incentives for manufactures to perform studies for the additional label claims.[26] There are drugs that when used off-label can be harmful. For example, pain relievers such as ibuprofen can cause severe side effects in cats.[34]

Due to the varying advantages and disadvantages of off-label use of drug products in human and animal medicine, the government should not impose undue regulation to standardize the issue. It is best left up to the practice of medicine with the physician or veterinarian experience with the drugs in the field to make the judgment as the current practice is today. The FDA needs to balance necessary regulations without causing unnecessary interference.

Health Insurance

Another difference between human drug industry and animal health sector is in how the drug is purchased and paid for. As of 2014, the Affordable Care Act required every human to have health insurance, or would face a penalty.[44] Health care insurance helps off-set the costs of medications for humans. Animal health insurance is available, but there is no requirement for animal health insurance. Only a small percentage (2%) of people in the US has health insurance for pets.[32] For human pharmaceuticals, depending on the policy, a portion of the medication is

paid for by insurance, and the patient has to pay their portion when receiving the medication. However, insurance companies will reimburse patients only for drugs that have been approved by the FDA for the use in which they are prescribed.[44]

Unlike human insurance, animal health insurance is a reimbursement based program. A pet owner must first pay the vet bill, submit the claim to the insurance company and then receive reimbursement. The reimbursement for animal health care can be up to 90% of the healthcare bill.[45]

CHAPTER THREE: METHODOLOGY

To collect and systematically analyze the information about off-label use of human drugs in animals in regards to their economic benefit use versus the approved use, a quantitative and qualitative study was conducted in January 2015. There were two aspects to the study; factual based information about costs and revenues obtained from published literature, and opinion based information from the general public. This information had to be collected and analyzed differently in order to provide comprehensive results and discussion.

For the first aspect, a literature review was conducted to determine the factual data on costs for developing human and animal drugs, as well as revenues received by human and animal pharmaceutical drugs. Human drug revenues were reviewed to determine the revenues received from off-label use in the animal pharmaceutical industry as well as the frequency of use in the animal health industry. Company annual reports from human pharmaceutical companies, as well as veterinary medical supplies, were reviewed to determine the revenues received from off-label prescriptions of human drugs in animal health. For the second aspect, a study was conducted through means of a survey and individual interviews with the general public to gather opinions on the use of human drugs off-label in animal health. In order to conduct the survey and interviews, approval was received through the Institutional Review Board (IRB) from the University of Georgia in compliance with Title 45 Code of Federal Regulations Part 46.[46] The approval was granted on January 12, 2015, under the IRB ID STUDY000001678.

For the literature review, research was conducted on the internet through scholarly articles, annual company reports and other forums which provided financial data for both human and animal pharmaceutical manufacturing companies, along with human and veterinary pharmacies. The financial data was reviewed for the costs of bringing human drug products and animal drug products to market. Information on revenues that a human drug manufacture receives from the off-label use in the animal health field was also reviewed.

In order to gather the quantitative data from opinions, a survey was developed to ask questions of the general population on off-label use of human drugs in animals, and responders' opinions on their willingness to potentially pay more for an animal drug. The survey was conducted with individuals who met the inclusion criteria of the study. The inclusion criteria required that the participants were:

- At least the age of 18 or older
- Lived in the United States
- Own companion animals and/or
- Work in the human or animal pharmaceutical industries.

The exclusion criteria for the survey participants were:

- Under the age of 18
- Living outside of the United States
- Did not own pets and did not work in the animal or human pharmaceutical industry

The first questions within the survey were created to screen the participants for their eligibility based on the inclusion/exclusion criteria. If the participant did not meet the requirements, the survey ended. In the first question, participants had to identify their age group.

If the response was under 18 years of age, the survey was concluded for that subject. For the second question, if the participant answered that they do not reside in the United States, the survey ended. For question three, if the respondent answered "no" to having owned pets, and did not select that they work in the animal health industry or human health industry in question seven, the survey ended. Demographic questions were developed based on age, education and occupation to be used in the statistical analysis to determine if there was statistical significance between the groups. The remaining questions were used to gain knowledge on participants' opinions on the use of human drugs in animal health.

According to the Humane Society of the United States, approximately 62% of all households owned at least one pet in 2012.[47] According to American Veterinary Medical Association (AVMA), there are approximately 99,720 veterinarians in the United States from 2012-2013.[48] The population exceeds into millions, and would have been impossible to survey the entire population due to time and budget constraints. Response rates tend to be approximately 20%, depending on the content and length of the questionnaire. A large broadcast of the survey was required using the survey for two main reasons: (1) to ensure that the demographic profile of survey respondents reflects the survey population; and (2) to provide a sufficiently large data set for analysis.[49] A study sample size was calculated to be stratified based on level of education to address the demographic profile of the US. There were four groups based on the highest level of educational attained as the sample has to be representative of the larger population to obtain a compatible profile of the population.[49] Education is important in order to obtain reliable answers in any survey according to other studies using education as a demographic.[50]

Following the population distribution based on the US Census, approximately 46% of the population had a high school diploma or equivalent as their highest level of educational

attainment, 7.5% of the population had an associate's degree, 18% had a bachelor's degree, 7.2% had a Master's degree, and 3.1% had a Professional or doctoral degree.[51] The survey attempted to reach 50-100 participants to achieve a 95% confidence level with an alpha level of 0.05. The calculation for this participation is found later in this chapter and is accompanied with Table 2. The targeted population of the survey respondents was designed to model the US population based on their educational attainment as this is believed to be a major variable in how respondents will answer the survey questions. The model attempted to reach a population with approximately 46% of respondents with the highest level of education a high school diploma, 7.5% of respondents with an associate's degree, 18% of respondents with the highest level of education an undergraduate degree, 7.5% of respondents with the highest level of education a graduate degree, and 3% of respondents with a professional or doctoral degree.

To determine the type of tool used for the survey, an assessment of the survey tools SurveyMonkey and Qualtrics was performed in order to determine the best method. The tool needed to be accessible through the internet, and provide security of the participant's information. In addition to these aspects, several of the questions provided in the survey required skip logic, where depending on how the respondent answers previous questions, the subsequent questions would change. An example of this was in the questions aimed specifically for veterinarians. The participants had to select that they had a Doctorate of Veterinary Medicine (DVM) in order to have the question of prescribing human products off-label for their clients.

In the review of SurveyMonkey, this tool met requirements except for the limit on skip logic of questions, numbers of questions that could be provided in the survey and formatting of the participant interface. There were multiple questions that needed more than one skip logic applied, and SurveyMonkey was not capable of that function. The more complicated skip logic

question revolved around the inclusion criteria that the participant either 1) needed to be a pet owner by answering ‘yes’ to owning pets, or 2) the participant did not have to be a pet owner by indicating ‘no’ to owning pets, but needed to be within the animal health or human health industry by indicating the industry that they currently work in; human or animal health. The free version of the SurveyMonkey software did not allow for customization of colors and fonts, and limited the number of questions to 10 per survey. The SurveyMonkey tool did not allow for changing colors or changing of the footer advertisement for SurveyMonkey making the view of what participants see while taking the survey unappealing and unprofessional.

UGA had a Qualtrics account, and could provide free access to the tool. There were no limits to skip logic questions, and no limits to the numbers of questions that could be asked in a given survey. The format presented nicely with the UGA branding and coloring. Based on the review, the tool used to collect the survey information was determined to be Qualtrics.

The tool was validated by using a sample of individuals that tested the usability, time and the general content of the questions. The sample group data received from testing the tool was removed from the data analysis. The Qualtrics tool also allowed for testing the survey by randomly applying answers for a specified number of runs. This was conducted with 25 runs of the survey to ensure the question skip logic did in fact work.

Access to Qualtrics was provided through the University of Georgia and did not require the participants to have a UGA account in order to answer the survey. The first page of the survey was for the informed consent; if the participant answered that they did not agree to participate, the survey ended. Responses were received in real time and saved in the Qualtrics system. The Qualtrics survey tool provided a reporting section with limited statistical analysis tools that were not appropriate in order to analyze the data. Raw data was downloaded in Excel

form and analyzed within SAS (Statistical Analysis System). SAS was used because it provides reliable results by using coding which has been verified to meet governmental compliance requirements.[52]

Per the study protocol, if any data was collected from individuals who later decided to discontinue their consent to participate in the study, that data would be deleted/destroyed and not used in the data analysis. No participants requested the removal of their data or participation. For those participants that completed the survey, their information will be kept for two years following the end of the study as specified in the protocol. Anonymity was maintained for the participants in the survey as no personal or identifiable information about the participants was collected. The raw data will only be visible to the principle investigator and researcher and the results were only provided in summary form for the thesis.

The data for the differences between groups of education, age and number of pets owned was analyzed through Fisher's Exact tests. The Fisher's Exact test is a type of Chi Square test used to analyze many surveys as it determines if there is dependence between two classification variables.[53] Therefore, the Fisher's Exact test was chosen to test whether the distribution of the set of data followed a particular pattern in regards to their willingness to potentially pay more for animal drug products. Using Open source Epidemiologic Statistics for Public Health (Open-epi) software that is available through Emory, the sample size needed to reach the 95% confidence level was calculated at 73 as shown in Table 2. This is why the decision of 50-100 participants was concluded for the survey sample size.

TABLE 2: Sample Size Calculation[54]

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	95%+/-5
Confidence limits as % of 100(absolute +/- %)(*d*):	5%
Design effect (for cluster surveys-*DEFF*):	1

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	73
80%	32
90%	52
97%	90
99%	127
99.9%	206
99.99%	288

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

Three variables were compared to determine if there was statistical significance in the demographics of the population when it came to their willingness to potentially pay more for an animal approved product. The first aspect considered was the level of education of the participants. The null hypothesis for the statistical analysis was that there would be no difference between levels of education and the participant's willingness to potentially pay more for an animal approved product. The alternative hypothesis was that there would be a statistically significant difference between the levels of education. The second aspect reviewed the age of the participants. The null hypothesis was that there would not be a difference between the age groups of the participants, while the alternative hypothesis would be that there was a statistically significant difference in age groups. The third aspect analyzed the numbers of pets a person owned. This analysis was performed to determine if there was a statistically significant

difference between the numbers of pets a participant owned and their willingness to potentially pay more for an animal approved drug product.

In addition to the survey, a randomized group of individuals were contacted to participate in individual interviews for the study. These individuals did not respond to the survey to reduce duplication of answers. These individuals were contacted through email and were required to sign an informed consent prior to answering interview questions. Once the informed consent forms were signed and obtained by the researcher, the participants were contacted and a time was scheduled for the interview that worked for both the researcher and the participant's schedule. The interviews were conducted either by phone or in person depending on the scheduling availability of the respondents. The interviews were based on the same questions available in the survey, but allowed the flexibility to ask more details to why participants responded the way they did. As with the survey, any data collected from individuals who later decided to discontinue their consent to participate in the study would be deleted/destroyed and not used in the data analysis. No participants in the interviews requested their removal.

For those participants who elected to participate in the survey and interviews, their responses will be kept for a period of two years and will be stored on a password protected computer, visible to only the principle investigator and researcher. The data available in this thesis will be provided in summary form only. All data collected was saved on the researcher's flash drive which was stored separately from the computer in a locked filing cabinet not accessible to anyone else to maintain anonymity of the data from the survey and the interviews. Both the survey responses and the interview responses were collectively analyzed in order to answer the questions of this study.

Potential biases to be disclosed in this study include the use of social media to recruit survey participants, as well as recruiting interview participants through email since only a subset of the sample population had access to the study. Since the survey was only available through social media, the population in the United States that do not participate in social media were not aware of the survey's existence and did not have a chance to offer their opinion. By only providing the request for interviews through email, this also ignored individuals that do not use email. Therefore any conclusions made from the data findings in this study will only be applicable to the populations of social media users and those that use email; not the entire population of the United States.

Recruitment

In order to have participants involved in the survey, social media was used to encourage participation of individuals with no personal affiliation with the research investigator. After the protocol was approved by the IRB, the recruitment began on January 12, 2015. The recruitment statement was posted on several social media group pages through Facebook and LinkedIn. The targeted response for this study was for a range of 50-100 participants. This sample size was targeted in order to achieve a 95% confidence interval. The survey was published to more than 900 individuals (over 700 through LinkedIn users, and over 200 Facebook users) and was made available for 3 weeks per the approved IRB protocol. At the end of the three week time period, the survey was closed and final data were extracted to complete the analysis.

At the end of the three week period, there were 131 total responses to the survey. Out of 131 responses, one participant declined to participate in the study, and two participants stopped

after answering their age group and if they owned pets. Two participants were located outside of the United States which did not meet the inclusion criteria. There were 12 participants that did not own pets, and did not work in either the human or animal pharmaceutical industry. These participants did not meet the inclusion criteria and were removed from the analysis. Out of 131 individuals that started participation in the study, 114 met inclusion criteria. Out of the 114 participants, 20 participants did not fully complete the survey. Therefore there were a total of 94 participants completed the survey. The 20 participants that did not complete the survey impacted the results and the ability to use the Fisher's Exact test which will be discussed in the method of analysis section.

For the interview requests, random individuals were emailed for participation in the study. Twenty random individuals were contacted through email with the target of completing ten interviews. Out of those contacted, seven individuals agreed to participate. The participants completed an informed consent form, and were contacted to set up the interviews. The interviews were scheduled starting from January 12, 2015, and were conducted until February 2nd, 2015. Prior to the interview questions, participants were briefed on the background and initiative to complete the study. The interviews lasted approximately thirty minutes each, and provided details that were not available in the survey responses. Following the three week period of interviews, the study was completed on 2 February 2015 per the IRB protocol.

Analysis

After the completion of the literature review, survey and interviews, all data were collected and systematically analyzed. The data from the literature review was evaluated for the cost analysis. The literature review concerned annual reports of leading human pharmaceutical

companies, veterinary pharmaceutical companies and veterinary supply companies. While there was an abundance of summarized data on these companies' financial earnings, the breakdown and availability of off-label prescribing revenues was not as readily available. There are several avenues in which the drug will reach the pet owner. Since veterinarians generally use veterinary supply companies to obtain human pharmaceuticals for their practice, a review of veterinary supply companies was perfumed. Their annual reports did not provide a breakdown of the actual spending per human pharmaceuticals. However, one survey was found that reviewed several veterinary supply companies that did indicate the amount of expenditure per dog that was actually spent towards human pharmaceuticals.

The data from the survey was analyzed by looking at the overall statistical significance, of whether a individual's education, age or number of pets owned influenced their decision to spend on their pets, while also looking at a granular level of responses by looking at each individual response in the open text fields in the survey in relation to the overall summary of data. The question on pet owner's awareness of medications their pets were currently taking was reviewed to determine if pet owners knew if their pet medications were human medications. For the individual survey responses where open ended text was provided, the researcher reviewed the additional details in order to understand why participants answered in the way that they did. These open ended responses helped the researcher better understand the relationship of the responses and provide for a more thorough discussion of the results.

The results from the interviews were collected and reviewed to aid in making a more comprehensive interpretation of the personal opinions of the same questions provided in the survey. In the interviews, additional questions were asked depending on the way the participant responded to the questions. While the interview responses were not quantitative in nature, they

provided qualitative information to enhance the discussion of the research topic being addressed. The interview questions were similar to the survey questions which allowed the interview participants to provide a reason for each of their responses. The answers from the interview participants were then correlated with the survey responses to aid in the discussion of these topics.

By combining the literature review, survey results and interview responses, this study intends to answer the original questions addressed in this study.

CHAPTER FOUR: RESULTS

Following the execution of the study, the data were compiled from the literature research, survey responses and interview responses. The following provides the results for each of these components of the research study.

Literature Review Results

A literature review was conducted to answer the question if it is worth the time and cost to bring an animal product to market when there already is a human drug product available and used in animal health. Revenues of the top five human and animal pharmaceutical companies were reviewed, along with the average cost and time it takes to receive an approval for an animal drug. The information on potential revenues human drug manufactures make from their products being used in animal health was not readily available. In order to make an estimate of this cost, a review was conducted on the yearly expenditure on animal drug products for companion animals, numbers of companion animals owned, and the avenues in which pet owners receive their drug products. The 2013 revenues for both human and animal pharmaceutical companies are presented in Table 3. The 2013 data was used since the data for 2014 was not yet complete at the time of the review for all companies. This table shows that human pharmaceutical companies make far more than animal health.

TABLE 3: Revenues of the Top Five Human and Animal Pharmaceutical Companies

Human Pharmaceutical Company	Revenue 2013 (In US Dollars)[55]	Animal Pharmaceutical Company	Revenue 2013 (In US Dollars)[30]
1. Johnson & Johnson	71.31 Billion	**1. Zoetis**	4.56 Billion
2. Novartis	57.92 Billion	**2. Merck Animal Health**	2.36 Billion
3. Roche	52.31 Billion	**3. Merial**	2.73 Billion
4. Pfizer	51.6 Billion	**4. Elanco**	2.15 Billion
5. Sanofi	45.01 Billion	**5. Bayer Animal Health**	1.8 Billion

The average cost and time to bring an animal drug product to market was determined by averaging three different sources (Table 4). In the review of the literature, the average costs to receive an animal drug approval was approximately $100 to 200 million, and the time to bring an animal health product from the research table to shelf was approximately 7 to 12 years. This is why it is important for the drug that an animal health company manufactures has the ability to bring in revenue over $200 million in order for the company to pay for the original investment, and then to make a profitable business. Therefore, if the revenue a human company makes from a product that is used in animal health is greater than the $200 million, it will be worth the expenditure. If the profit is not greater than $200 million, then it is not worth the cost and time.

TABLE 4: Time and Costs for an Animal Drug Approval

Source	Cost	Time
AHI Doctor Testimony[51]	100 Million USD	7-10 years
AVMA[20]	Up to 200 Million USD	7-10 years
Animal Health Markets[1]	200 Million USD	8-12 years

In the Pet Industry Market Size and Ownership Statistics, the overall spending on pets in the United States in 2013 was approximately 55.72 Billion USD.[57] This number includes supplies, food, surgeries, boarding, medicine and veterinary care. Out of this total reporting, the most important number to this research was the amount spent on medicine and veterinary care as

this describes the costs pet owners spend on medication for their animals. Veterinary care in this survey included veterinary visits and prescription medications. The table below shows the expenditure in US Dollars:

TABLE 5: Type of Expenditures and US Dollar Amounts

Type	Expenditure
Supplies and OTC Medicine	13.14 Billion
Vet Care	14.37 Billion

The amount of spending per companion animal species per year was found to be approximately 231 dollars per dog and 193 dollars per cat.[57] For horses, it can cost approximately 300 dollars a year for a healthy horse.[58] These numbers are only associated with standard yearly vaccines and worming medications and does not include other expenses such as boarding and feeding. The total numbers of pets owned in the United States in 2013 was approximately 396 million.[57] The table below shows the breakdown of that number in regards to the companion animals in scope of this research.

TABLE 6: Numbers of Pets owned by Species in the US

Species	Numbers Owned[57]
Cat	95.6 million
Dog	83.3 million
Horse	8.3 million

There are several avenues in which a drug product travels from the manufacture to reach the pet owner. Because of these broad avenues, as well as other factors, the assessment of the actual revenue a human drug manufacture receives from products used off-label in animal health was difficult to obtain. The following figure shows a high level view of the supply chain for pet owners to obtain products for their animals.

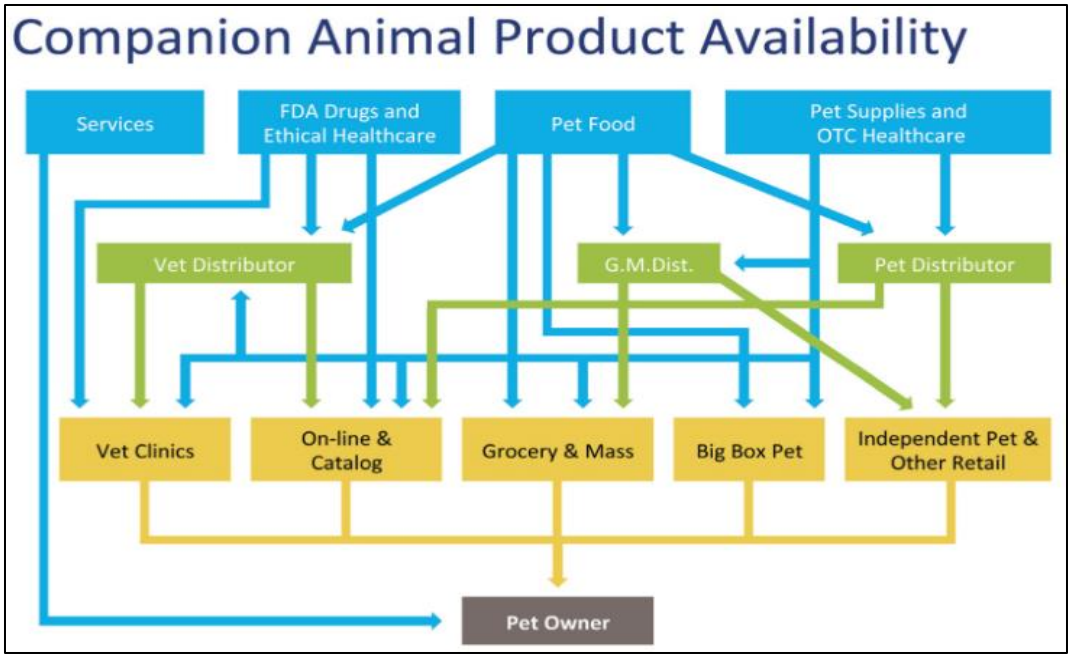


FIGURE 3: Supply-chain landscape for animal health, BRAKKE Consulting[59]

In addition to the extensive supply chains, the off-label prescribing frequency is not effectively documented in previous literature and not widely available. In order to assess the amount of revenue a human labeled product generates when used in the companion animal field, a review of veterinary supply companies was conducted. A survey was conducted by Animalytix LLC through distributors of veterinary supplies in 2012. Out of this survey of veterinary suppliers, approximately 190 million US dollars in annual sales came from human labeled Pharma products.[60] The survey also shows an allocation of expenditure per dog for off-label use of human pharmaceuticals, only focusing on "cared for" dogs which was defined as animals that have had annual DAP vaccinations (vaccines against canine distemper, canine adenovirus, and canine parvovirus). In 2012, approximately 2 to 10 dollars out of a total of 12 to 45 dollars spent on dogs (respectfully) in regards to medications were spent on human pharmaceuticals. The highest expenditure was in Minnesota at 20 dollars per a total expenditure of 35 dollars per dog.

Information broken down on the expenditure per cat or horse was not available. Figure 4 below shows a detailed summary from the survey developed by Animalytix.

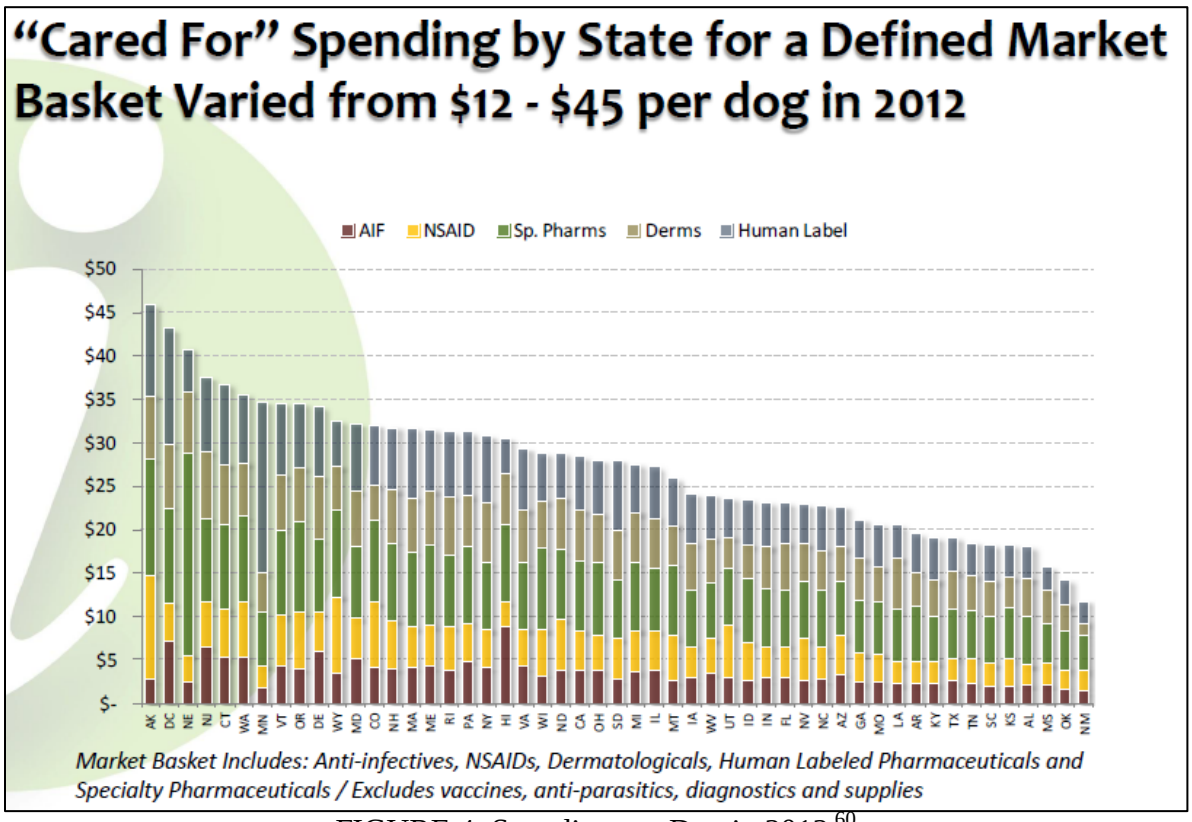


FIGURE 4: Spending per Dog in 2012 [60]

There was a report in 2011 that indicated Americans spent nearly $7 Billion on psychiatric human pills for their pets. This number was up 35% in four years.[33] If the rate of growth continued at 35% since 2011, it could mean nearly $9.5 billion will be spent towards psychiatric pills in 2015. Since psychiatric medicine is not the only type of medication used off-label for animals, the amount of actual spending on human products used off-label in animals could potentially be higher.

Survey Results

In order to evaluate the public opinion on the off-label use of human drugs in animal health, a survey was conducted through social media groups on both Facebook and LinkedIn for a period of three weeks through the Qualtrics survey tool provided by the University of Georgia. The survey was conducted for participants that were age 18 or older, lived within the United States, and either had pets, and/or worked in the human and animal health industry. Out of the total 131 participants that attempted the survey, 114 qualified and began answering survey questions. Out of 131 participants, one participant declined to participate in the study, and two participants stopped after answering their age group and if they owned pets. Two participants were located outside of the United States which did not meet the inclusion criteria. There were 12 participants that did not own pets, and did not work in either the human or animal pharmaceutical industry. These participants did not meet the inclusion criteria and were removed from the analysis. A total of 114 participants qualified and started the survey, but there was a dropout rate of 18%, and therefore there were a total of 94 participants who completed the survey. Appendix 4 provides tables of the survey results in terms of demographics.

The age distribution in the survey provides representation from all age groups classified in the study. The majority of the respondents were within the age rages of 26 to 35 (28 out of 114 participants) and 46 to 55 (32 out of 114 participants) years of age, the third group was the 36 to 45 (20 out of 114 participants) and the lowest participation was within the 18-25 age group (9 out of 114 participants). In terms of highest level of educational attainment, the majority (49%) of participants had a bachelor's degree. The other educational categories represented were the were High school/GED (18%), Associates degree (16%), Master's Degree (13%) and the

smallest categories represented were in the PhD and DVM education categories (4%). The population that was originally targeted was to be a distribution closely resembling the United States population with 46% of respondents with a high school diploma/GED, 7.5% of respondents with an Associate's degree, 18% with an Undergraduate/Bachelor's degree, 7.5% with a graduate degree, and 3% of respondents with a doctoral degree. Interestingly, the percentages for High school/GED and Undergraduate/Bachelor's degree where reversed. The actual population participating in the survey had a much higher percentage of Bachelor's degrees than the US population. The Associates and Masters degrees were about double the percentage of the US population, while the doctoral degrees were represented approximately in the same manner as the US population. The survey population was more highly educated than the typical distribution of the US population.

The majority of the participants worked in industries other than human and animal health industries (75%). Of this 75%, the common industries reported by participants in the open text field described that they were in accounting, education, electronics, finance, information technology industries, real-estate, along with many more categories with less frequency. The rest of the participants worked in the industry categories of animal health (8%), human health (13%) and were considered full time students (4%). The numbers of pets owned by participants fell heavily in the one to three pets category (77%), while the second highest category was in the 4 to 6 pets range (14%). The numbers of participants owning 7 or more pets (6%), or no pets at all (3%) were much smaller.

The following provides a narrative explaining the distribution of responses to the survey questions along with a visual figure.

Participants were asked if they were giving their pets medicine, if they were aware of any medications their pets were currently taking were approved by the FDA for use in their animal or if they were human medications (Figure 5). Of the 112 participants that owned pets, 108 participants answered the question. A small percentage of participants were not sure if the medication they provided to their pet were approved for humans or if they were approved for animals (8%). Of the nine participants that were not sure, three respondents reported using fluoxetine or Benadryl which are human drug products. Thirty-one percent of participants were providing medications to their pets, and reported that they were aware if the medication was used off-label. In the open text field, 35 participants provided the names of the drugs they gave to their pets. Some of the reported human drugs being used for the participants' animals include Benadryl (1), Fluoxetine (1), Meclizine (1), Robitussin (1), and Zyrtec (1).

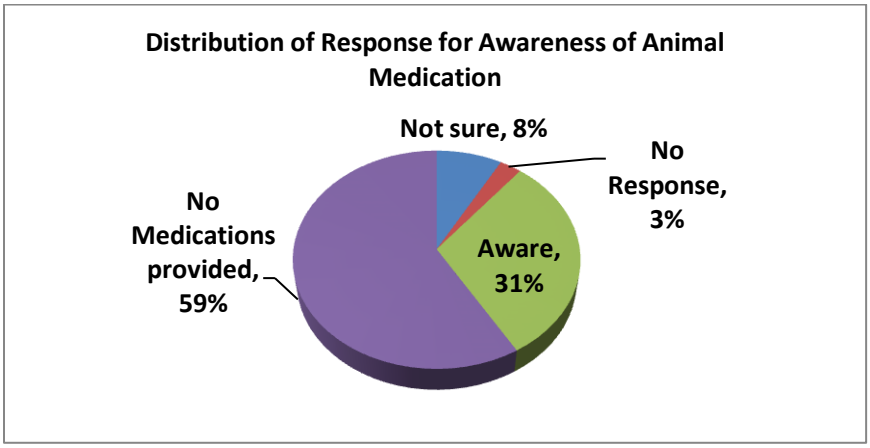


FIGURE 5: Response Distribution: Awareness of Animal Medication

Participants were asked if they thought veterinarians should be able to prescribe human drugs off-label to their pets (Figure 6). A total of 111 participants responded to this question. There were three participants that dropped out of the survey at this point. Fifty-five participants

responded ‘yes’ that veterinarians should be able to prescribe drugs off-label for their pets, while fifty-six participants responded ‘no’. The responses were evenly split.

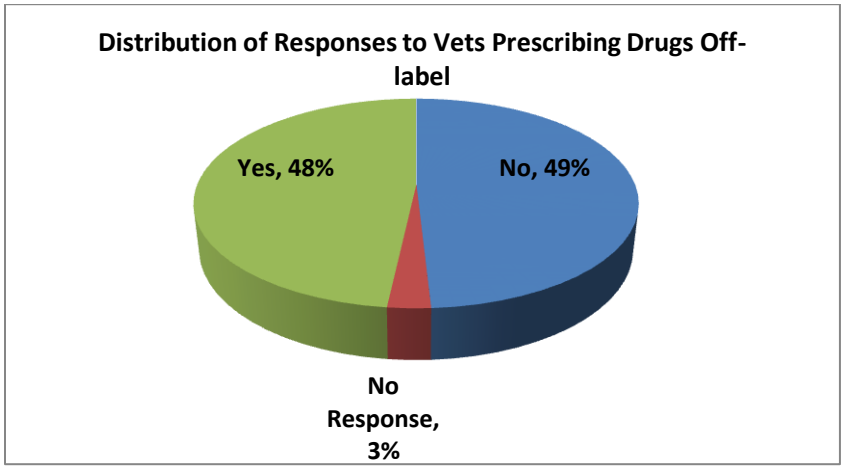


FIGURE 6: Response Distribution: Vets Prescribing Off-label

Participants were asked if the FDA should require that all drugs a veterinarian could prescribe to pets need to be approved by the FDA for their animal’s species (Figure 7). A total of 94 participants answered this question. Between this question and the previous question, 17 participants dropped out. These 94 participants continued to answer the entire survey and no more drop outs occurred. The majority of participants (61) responded ‘yes’, that the FDA should require approval of a product for the animal before a veterinarian can prescribe a drug product to their pets, while 33 participants answered ‘no’.

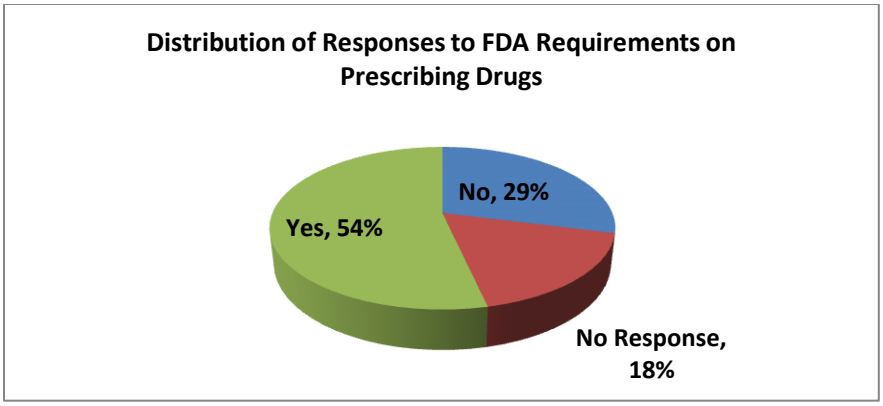


FIGURE 7: Response Distribution: FDA Requirements on Prescribing Drugs

Participants were then asked if the FDA does not require that the drug is approved for animal use before a veterinarian can prescribe them, then why did any drugs need FDA approval. Table 7 below provides a sample of the open text responses from participants on why they believe FDA approval of drugs is or is not necessary.

TABLE 7: Open Text Responses to FDA Requiring Approval of Drugs

	Open Text Responses
In favor of FDA approval	• "All animal species are different" • "I would imagine that different species can react differently to drugs, from it being completely ineffective to experiencing negative side effects. As a pet parent, I feel there should be regulation so that my pets are receiving proven care and are not subjected to experimental prescriptions/dosages." • "To ensure it's "safe." • "I want to know certain precautions were in place and regulated when the drug was manufactured."
Not in favor of FDA approval	• "I don't think we need the FDA at all." • "I do not think it should" • "I don't think the FDA should be involved at all"

There were additional questions provided in the survey that were only open for those that either responded to being a veterinarian or working in the animal health industry in the

demographic question at the beginning of the survey. If the participant answered that they were a veterinarian, they were asked if they prescribe drugs off-label to clients, which drugs they tend to prescribe, if they believed their clients would be willing to spend more on their animal medication if it had an animal approved label, and if it would be worth the investment for the animal drug company to develop these animal approved drugs. There was one veterinarian that responded to the survey and was prompted to answer these questions. The veterinarian responded that he/she did prescribe drugs off-label to clients, and they referenced linezolid as a product they prescribed to their animal patients. When asked if he/she believed that their clients would pay more, the veterinarians responded that the clients would be willing to pay more "depend[ing] on client values, socioeconomic status, and the specific drug and disease condition".

The final question was a yes or no question that asked if the participant believed it was worth it to the animal health company to receive the animal approved label for the human drug product. This question was opened for veterinarians and those that responded as working in the animal health industry. The veterinarian responded with 'yes' the amount of cost and time is well justified for the amount of income it can bring to the company. For the nine participants that responded to working in the animal health industry, they were also asked the additional question if it was worth the cost and time to bring the animal drug approved label to market. Six respondents answered yes (66%), while three responded no (33%).

The survey questions up to this point were to gather general knowledge about the public's awareness to their pet's medications, their opinions on veterinarians prescribing drugs off-label, and their opinions on FDA requirements of approval for drugs to be used on their pets. The targeted questions for the veterinarians and animal health industry participants were used to gather knowledge of the opinions of those that work within the animal health industry. The

following question was used to answer the main question of the thesis; if pet owners were willing to pay more for medications for their pets for an animal approved product, versus the off-label use of the human drug. Statistics were calculated for this question to provide support for the discussion.

Participants were asked if they were willing to potentially pay more for a drug with an animal approved label versus paying less for a human drug product for their pet (Figure 8). The majority of the participants (65) said yes, they would be willing to pay more for an animal approved drug product while 29 participants said no. If taking out the number of non-respondents (18%), then 69% out of 94 responses said yes, and 31% of the 94 responses said no.

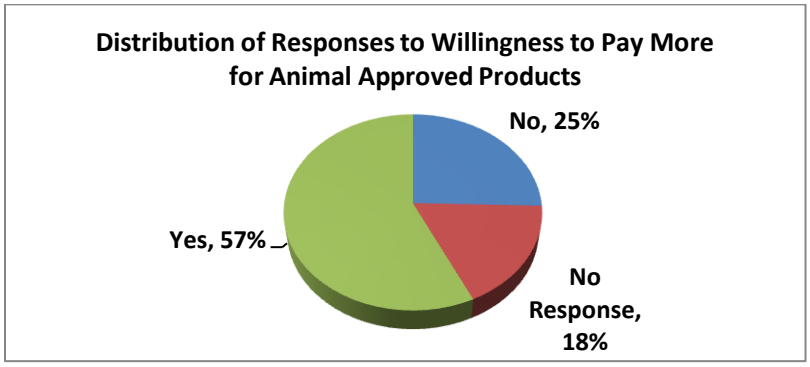


FIGURE 8: Response Distribution: Willingness to Pay More for Animal Approved Products

The participants were provided an open text field to explain their reasoning for answering the question on willingness to pay more for their animal drugs. Table 8 below shows a sample of the responses in an open text field provided by the participants.

TABLE 8: Open Text Response to Willingness to Pay More for an Animal Approved Drug

Response	Open Text Response
Yes	• "I would rather pay more for something I know that is going to work for my pet so that I know that the medicine will help them to get better." • "Would make me feel more confident" • "I would like to put my dollars toward research. If that means paying more I am fine with that." • "knowing that the medications has proven to work for my animal is worth the extra expense" • "I would pay more knowing that my pet would not experience bad side effects from the meds. I won't pay an extreme increase in costs of medication though. There is a limit." • "Assurance of both safety and effectiveness by species, size, age, etc."
No	• "I trust the free market" • "If it is approved for humans, it is usually already animal safe" • "Dog insurance does not really cover meds, their meds a[re] very expensive… money is tight" • "I already give them Benadryl for humans. I feel it is just another way for them to charge more

This survey question aimed to answer the question first proposed in this research; if pet owners are willing to spend more on an animal labeled product when a human drug product is available for use. Three variables were considered to possibly influence the way in which a participant may respond to this question. To determine if there was statistical significance of willingness to pay more based on three variables age, education and number of pets owned, the data was analyzed through SAS by using the Fisher's exact Test. This test was used for the discrete data of yes or no, and due to the low frequency of respondents in sub-categories within age, education and number of pets owned. There were 20 participants that did not answer the question which prompted the warning seen in the statistical tables. The overall findings showed that at a 95% confidence level, both variables of age ($p=0.75$) and education ($p=0.89$) did not significantly influence the way participants answered this question. These tables can be found in

Appendix 5. However, the numbers of pets owned did show that there was statistical significance between the population groups at the 95% confidence level (p = 0.03) (Table 8).

TABLE 9: Fisher's Exact Test for the Numbersof Pets owned versus Response to Willingness to Pay

Statistics for Table of PET_NUMBER by PAY

Statistic	DF	Value	Prob
Chi-Square	3	7.5243	0.0569
Likelihood Ratio Chi-Square	3	8.2030	0.0420
Mantel-Haenszel Chi-Square	1	0.7459	0.3878
Phi Coefficient		0.2829	
Contingency Coefficient		0.2722	
Cramer's V		0.2829	
WARNING: 63% of the cells have expected counts less than 5. Chi-Square may not be a valid test.			

Fisher's Exact Test	
Table Probability (P)	0.0011
Pr <= P	0.0337

Effective Sample Size = 94
Frequency Missing = 20

WARNING: 18% of the data are missing.

For pet owners who had 1 to 3 pets, 49 out of 72 participants agreed that they would be willing to pay more on their pets versus 23 that did not. For the pet owners in the category of 4 to 6 pets, 13 agreed that they would pay more for their pets versus 1 that did not agree to pay more. Both of these categories greatly favored the "yes" they would be willing to pay more on an animal approved product. For the category of 7+ pets and no pets (None), the results appear to be split. For the 7+ category three participants responded no, that they would not be willing to spend more versus two that would be willing to spend more. For the participants who did not have pets (None), two responded that they would not be willing to pay more, while one responded that they would be willing to spend more. There was not an overwhelming majority compared to the 1 to 3 and the 4 to 6 category. Table 10 below shows the frequency in which respondents answered based on the number of pets owned.

TABLE 10: Frequency of Number of Pets Owned versus Responses to Willingness to Pay

Frequency Percent Row Pct Col Pct	Table of PET_NUMBER by PAY		
PET_NUMBER(PET NUMBER)	PAY(PAY)		
	No	Yes	Total
1 to 3	23 24.47 31.94 79.31	49 52.13 68.06 75.38	72 76.60
4 to 6	1 1.06 7.14 3.45	13 13.83 92.86 20.00	14 14.89
7+	3 3.19 60.00 10.34	2 2.13 40.00 3.08	5 5.32
None	2 2.13 66.67 6.90	1 1.06 33.33 1.54	3 3.19
Total	29 30.85	65 69.15	94 100.00
Frequency Missing = 20			

Interview Results

Interviews were conducted with pet owners, veterinary technicians, and veterinarians. In order to obtain interviews, emails were sent out to contacts of the researcher that had been a collection of colleagues over several years, college acquaintances, and several other personal contacts. Out of the 20 randomly selected email addresses that were contacted, seven potential interview candidates responded and signed an interview consent form. These seven potential participants were then contacted, and their eligibility was assessed. All seven potential participants meet the inclusion criteria of being 18 years of age or older, living within the United States, and they all owned pets. An interview was scheduled with each one either by phone or in person. The interviews did not include human pharmacists, FDA contacts, or human medical doctors that were contacted. Even with these limitations, the interviews that were conducted

provided general information on the frequency of off-label use, as well as the willingness of pet owners to pay more for the animal labeled products. While the interviews did not provide a large set of data on opinions, it provided more information than what currently existed.

The interview respondents included pet owners (4) working in various industries, and three participants working in the animal health industry; two veterinary technicians and one veterinarian. The four participants that were not in the animal health industry owned anywhere from 1 to 3 pets and had education ranging from bachelor's degree to a master's degree. The participants in the animal health industry also owned 1 to 3 pets and had education ranging from an associate's degree to a Doctorate of Veterinary Medicine. They were all asked the same questions as were asked in the survey, with some additional follow-up questions.

For the awareness of using a human drug medication, all participants were providing some type of animal approved drug. Only one participant was providing a human medication (fluoxetine for behavioral issues) and knew that it was a human drug being used off-label. This participant was not in the animal health industry.

The participants were asked if veterinarians should be able to prescribe human drug products off-label to animals. All participants answered yes, that veterinarians should be able to prescribe human drug products to animals. One participant said "I trust my vet to make the best decision for my dog" while another said that they "trust my vet more than I trust the FDA". The veterinarian and veterinary technicians were asked an additional follow up question of what medications they prescribe off-label. The products that were mentioned by the veterinary technicians and veterinarian included Enalapril, Fluoxetine, Omeprazole, Tamiflu, and Xanax.

Every participant did not believe that the FDA should require approval of the drug with an animal specific claim before the veterinarian could prescribe it to the animal. When the

participants classified as pet owners were asked why FDA approval is needed if veterinarians can prescribe products that are not approved for pets, one pet owner stated that "there has to be some form of safety and efficacy, even if it is not in the specific species"

When the participants were asked if they would be willing to pay more for the animal approved drug product, all but two participants said they would be willing to pay more for a drug product that had the animal approved label. Of the five participants that stated they would be willing to pay more, one participant in particular wanted to make a clarification that it depends on how much that monetary difference would be. She stated "If it is a ten dollar difference, then yes of course. If it is a $1,000 difference, then no." The veterinarian and the veterinary technicians were asked a follow up question on their opinion if clients would be willing to spend more on their pets for the animal approved drug. The veterinary technicians both stated that it depended on the pet owner and their circumstance. They were used to a range of different types of pet owners that would be willing pay anything for their pets to pet owners that would cut costs by any means necessary. The technicians attributed a pet owner's willingness to pay more for their pets depended on their income, and numbers of pets that they owned. Pet owners that had higher incomes in general spent more on their pets than individuals with less income, or multiple pets. The veterinarian that agreed to be interviewed had a distinctly different opinion on pet owner's willingness to pay more for animal approved drugs. Before the question was fully asked, the veterinarian said that "no pet owner would be willing to spend more on their pets if the human drug was available at a lower price". This was an opposite opinion from the veterinarian that responded to the survey. The veterinarian interviewed followed up on that statement and said that unless the drug had a better means of administration than the human drug product which would help the pet owner provide the drug an increase pet owner compliance, it would not be

cost effective for an animal health company to achieve an animal label when the human label is available. According to the veterinarian, making the administration easier for pet owners to provide to their pets would mean that pet owners will be more willing to provide the medication to their pets, and would help with compliance to treatment regimens.

One additional question was asked to both the veterinary technicians and the veterinarian. They were asked which areas of animal health are most lacking in approved animal drugs that are needed. The top areas mentioned were cardiac and behavioral drugs.

Limitations

Results from the literature research, survey responses and interviews provided an overview of the animal health industry in terms of costs, and public opinions. However, there were some limitations with the results. For the literature review, only one reported analysis of human drug revenues in animal health was provided for the revenues of veterinary supply companies. The data only showed a breakdown of revenues for "cared for dogs"; the true dollars spent on cats and horses was not available. Therefore the number truly spent on human pharmaceuticals in animal health is most likely higher than $190 million per year. In addition, this information was from 2012. With the animal health industry continuing to grow, this number also has the potential to have risen in the past couple years.

For the survey, the initial target population was for the range of 50-100 participants, which was achieved; however, there was a high dropout rate of 18%. The demographics of the age distribution showed a higher participation rate in the 26-35 and 46-55 age groups. This could be related to the researcher's personal connections with peers and coworkers mostly belonging to

these age groups. The sample size of pet owners that owned 7 or more pets was very small and may have limitations on this population of pet owners. Participants with levels of education at the level of PhD's, Pharmaceutical Doctors and Veterinarians were also under represented in this survey. For the interviews, only 7 consented to be interviewed. Out of these 7 participants, only one veterinarian agreed to participate. This is considered a limitation as the goal was to ascertain a significant input from those who can prescribe drugs for animals in this study.

Due to these limitations, the data and conclusions cannot be generalized to a normal population and thus only apply to this study population. Even with these limitations, the data received from this study opens the door for additional research topics that can be explored with this interesting market in animal pharmaceuticals.

CHAPTER FIVE: DISCUSSION AND CONCLUSION

Animal health is very important to human health since animals are part of the food chain and serve as companion animals for many. There currently there is a shortage of drugs approved specifically for animal use. Veterinarians must sometimes use human drugs off-label to treat their patients in order to provide appropriate care. Off-label use of drug products is not illegal, as the FDA does not regulate the practice of medicine, only the actual claims a drug product purports to possess. With the animal health industry continuing to research for new animal drugs to add to their pipeline, a potential avenue could be to invest in the approval of drugs that already exists in the human drug side with an animal approved label claim. Since some of these drugs are already used in animal health in an off-label fashion, is it worth the research and development time and costs to receive the FDA's approval with the animal claim? With the potential of these animal approved drugs costing more than the human drug product in the market, will the consumers (pet owners) pay more? These two essential questions were the target of this study. It was hypothesized that it would be worth the cost and time to achieve an animal approved drug product and that pet owners would be willing to spend more on these products.

The results of the analysis of costs for the animal drug approval showed anywhere from $100 to $200 million. The time for the animal drug approval was found to be approximately 7 to 12 years. In order for the drug product to be worth the investment to an animal health company, the drug must not only cover the costs of research, but it must also make a profit. The time to invest in making the product should also not exceed the 7 to 12 years for approval. Therefore the

revenue that the human drug products are receiving from their use off-label in animal health must be greater than $200 million, and must take less than 12 years to develop and receive approval from the FDA. The revenue that the animal drug company develops needs to also be received before the drug goes off patent and has to deal with generic competition. As seen in the comparison of the revenues received by human drug manufactures compared to animal drug manufactures, there is quite a substantial difference. Since the animal drug manufacture has much smaller margins of revenue compared to the human drug manufactures, it is very important that the time and cost to develop these products with the animal approved claim must make a reasonable profit for these companies. The numbers of companion animals in the United States are in the millions, meaning that if products are made that provide a more successful treatment for these animals, the potential for revenue can be very valuable to animal drug manufactures.

While the exact revenues that human drug manufactures make on their products used off-label in animal health are not known, the results from veterinary supplier companies showed at least annual revenue of $190 million on human pharmaceutical products. Another report showed $7 Billion was spent on psychiatric human drugs in one year for animals. The $190 million is for revenues in 2012, so it may be assumed that the actual number would have increased in the past three years following the general trend of animal health +%2.[29] The $7 Billion spent on psychiatric drugs was reported in 2011, and could have also grown since this was first reported in 2011. At that point in 2011, the numbers had already grown 35% in the previous 4 years. If that same 35% growth continued, the potential for those sales in 2015 could reach $9.5 Billion. Since consumers can get drugs for their animals through other avenues the number still has the potential to be higher as these figures are not reported. At least for the revenue of one year in terms of numbers, it appears that it could be worth the initial cost and time of research and

development for an animal drug to be approved if the human drug is currently being used off-label in animals.

However, the simple comparison of numbers for cost and time alone cannot be the only aspect considered in order to justify whether it is worth the animal health company making these drugs directly for animals. Other aspects must be considered. For example, these human drugs are not made to be easily given to animals. The dosing size can be too large for the animal and needs to be cut down, the dose is in a coated tablet that will not dissolve before it goes through the animal's digestive system, or it could be in a form that is difficult to provide to animals. Due to these issues, pet owners are not likely to continue to give a drug when it is difficult to do so, and this also decreases compliance to the veterinarian's recommendation. Several ways of simplifying administration for pet owners that was recommended by the veterinarian in the interviews is the administration of the treatment in a way that is easier for the veterinarian or pet owner to provide. Routes of administration could be provided with food or in foods as chewable treats to make it easier to give to companion animals, or reducing treatment frequency can also be beneficial to help pet owners provide the drug to their animal and increase compliance and continued use of these drugs.

Another aspect to consider is that these drugs are not advertised and marketed for use in animals as this would be illegal. There is a potential for increasing the revenue amount when the animal claim is approved and the manufacture can legally advertise it for use in animals. Pharmaceutical companies spend a portion of their budget on advertising to bring in the big profits. If the advertising was applied to these human drug products for the approved animal use, these estimates of $190 Million and $7 Billion could again be much greater.

While the cost and time may be worth the investment, will the pet owners be willing to potentially pay extra for the product if the human drug is available at a lower cost? The results of the survey indicated that about six out of every nine respondents would be willing to pay more. Factors that were hypothesized to influence the participants' decisions were originally thought to be related to their education, age, and number of pets owned. Based on this research, the participants' education and age did not significantly influence how they responded to the question, but the numbers of pets owned did result in being statistically significant at the 95% confidence level ($p=.03$) to influence their answers. In this case, a higher percentage of participants owning between one and six pets were more willing to pay more for the animal approved drug as compared to those participants that either had seven or more pets or those that had no pets at all. It is understandable that a person owning seven or more pets may not be able to afford the higher cost drug for seven dependent pets as compared to a person that has fewer dependent pets.

Other results gathered from this survey are that about half of the participants believed that their vet should be able to prescribe drugs to their pets even through the FDA had not approved the drug for their species of animal. Interestingly, three respondents which were not sure if the medication they were providing to their pets was approved for use in animals were actually using human drug products. Out of those three respondents, two responded that the veterinarian should not be able to prescribe these drugs unless the FDA had approved it for use in their animals. It appears that some pet owners are not fully educated on the actual indications for the medications they are providing to their pets and the advantages and disadvantages of using human drug products off-label in animals. They are also not fully aware of the FDA's role in pharmaceutical product approvals. Educating pet owners on the medications they are providing to their animals

and making them aware of the reason behind the additional research for animal drugs in relation to their drugs cost may also help justify the production of these drugs by the animal drug manufacturer with the animal approved claim.

The results of the interviews were that five out of the seven participants were willing to potentially pay more for the animal approved drug versus the human approved drug. The two veterinary technicians agreed that certain pet owners would spend more, while others would not depending on their circumstances. These circumstances were associated with their income level and numbers of pets. There were a total of two veterinarians that responded to the study (one participated in the survey and one participated in an interview). These two veterinarians were polarized on their view towards clients spending more on an animal approved drug; one veterinarian felt strongly against the fact that pet owners would pay more, while the other veterinarian believed that depending on socioeconomic status and other factors, a pet owner would consider spending more on an animal drug product. With the results of the survey and interviews, it can be concluded that there is a potential value to have the animal approved drug product for the consumers as more than half would be willing to spend more on those products.

Several key factors were identified during the survey and the interviews that animal health companies need to take into account if making animal approved drugs from the current human drug products. These factors are (1) making the drug product easier to provide to animals such as chewables, (2) making drugs in a manner that can be provided less frequently, (3) the final cost of the product for the pet owner should not be excessively higher compared to the human drug product, (4) where current animal drugs are lacking (cardiac and behavioral drugs), and (5) pet owner education on (a) off-label prescribing, and (b) the importance of research and development in regards to species differences in animals.

Veterinarians have issues with their clients complying with their recommendation of continuing to provide medications to their pets. Therefore if the animal health company can provide a drug that is easily and readily accepted by animals, pet owners will be more likely to be compliant with their directions for use. Increasing compliance can also bring about re-purchasing of the product, making even more profit for the animal drug manufacture. As mentioned by one of the interview participants, the actual difference in cost between the human and animal approved drug would be important to know, and would change their opinion depending on how much that difference is. If the animal drug product will be substantially more in cost versus the human drug, pet owners may be more likely to get the human drug product.

Both the veterinarian and veterinary technicians pointed out that the areas that need more attention with animal approved drugs are in the areas of cardiac and behavioral drugs, and therefore should be areas of interest for animal drug companies to consider for potential expansion in their pipeline. Finally, pet owners are not always aware of the medications they are giving to their pets, and whether they are approved for use in animals or humans. They are also not aware of the importance of the FDA in protecting the health of our animals as seen by responses such as "I don't think we need the FDA at all". It is up to the industry, both animal drug manufactures and veterinarians to help ensure that pet owners are well educated on both of these factors so that they better understand the need for the approval of drugs specifically claiming to treat their animal's species.

In further support, animal health companies have already made products adapted for animal use from human drug products in the cases of the animal drug Palladia (Zoetis) and the human drug Gleevec (Novartis), the animal drug Reconcile (Elanco) and the human drug Prozac (Eli Lilly – parent company to Elanco) and several others. There are several other animal drug

manufactures that are working diligently right now in their pipeline on other new innovative animal drugs that are from the human drug collection. These companies include Kindred BioScience and Aratana which have publically stated the drugs that they have in their pipeline.

It is clear that there is a market for these drugs in animal health that are currently approved only for humans and used off-label in animals. If there was no market for these products, then these animal drug companies would not still be investing in development of these new products from the human drugs today like Kindred BioScience and Aratana. The actual revenue may not be precisely clear, but in general terms there is a value to develop these products, and based on the survey data, six out of every nine pet owners are willing to pay the added price, if it is within reason.

Further Research

Further research should be conducted to obtain a more exact estimate of how much revenue is received by human drug manufactures by product and by species of animal. This would help further refine the potential revenues an animal drug manufacture could make on receiving approvals of these human drugs with the animal claim. A broader survey of the public should be conducted to include more than social media users, and include a request for information on the participants' annual income. Research should also seek to include a greater sample of veterinarians and animal health professionals in the interview process. A person's annual income may influence how the consumer would be willing to spend their money on their pets, and would be interesting to know. By adding this additional data relevant to a person's annual income and broadening the broadcast of the survey, this would provide a larger sample in

which to make predictions on the true US population. Research should also be conducted to ascertain how much more money that pet owners would be willing to spend on their animal. These questions may also provide examples of diseases or ailments, the probability of surviving if given the treatment, and then the actual cost of the human drug, and the potential cost of the animal drug. The additional questions may help researchers better understand the degree to which the participants are willing to pay for their animal's health care.

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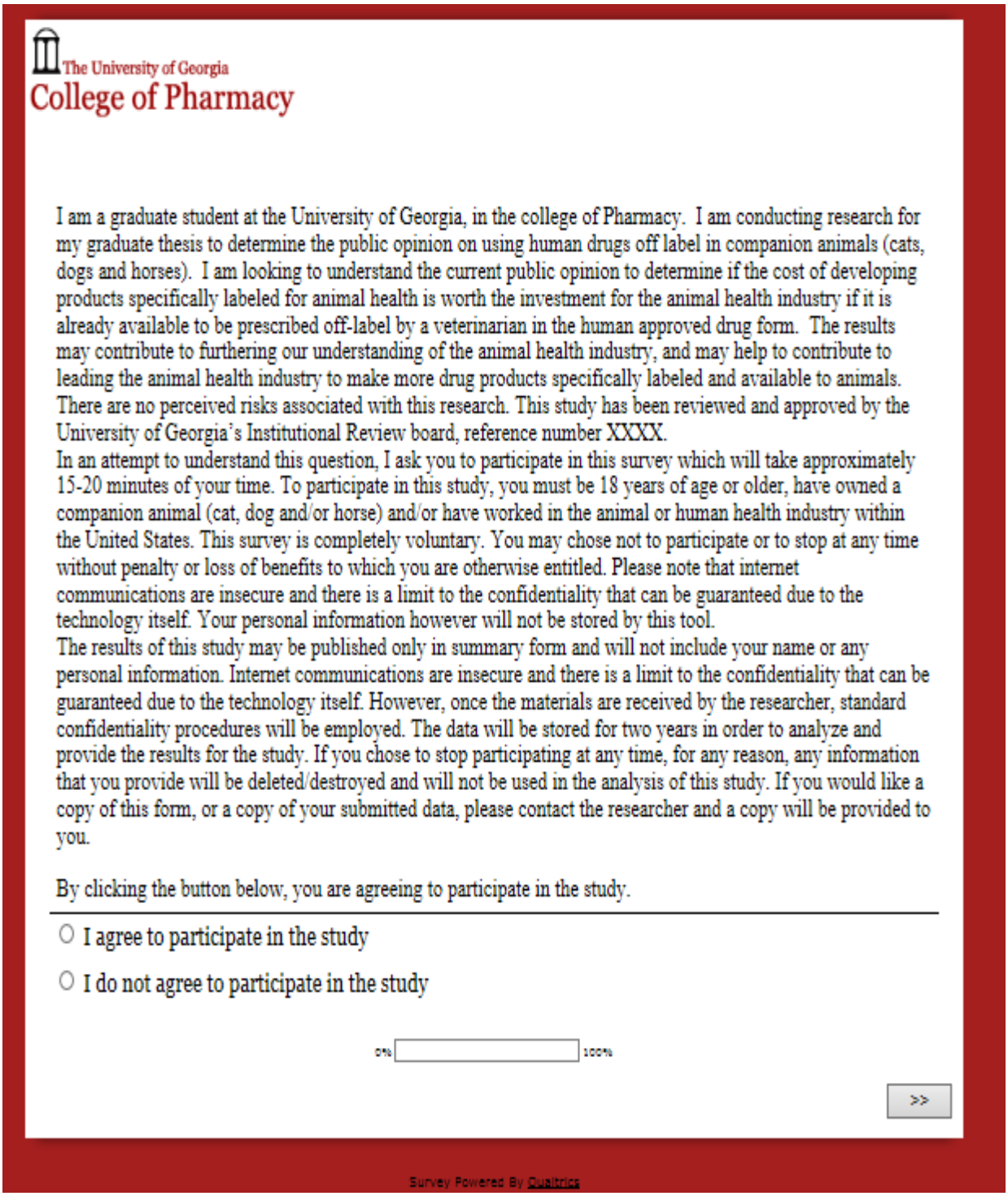
Appendix 1: Survey Questionnaire



The University of Georgia
College of Pharmacy

I am a graduate student at the University of Georgia, in the college of Pharmacy. I am conducting research for my graduate thesis to determine the public opinion on using human drugs off label in companion animals (cats, dogs and horses). I am looking to understand the current public opinion to determine if the cost of developing products specifically labeled for animal health is worth the investment for the animal health industry if it is already available to be prescribed off-label by a veterinarian in the human approved drug form. The results may contribute to furthering our understanding of the animal health industry, and may help to contribute to leading the animal health industry to make more drug products specifically labeled and available to animals. There are no perceived risks associated with this research. This study has been reviewed and approved by the University of Georgia's Institutional Review board, reference number XXXX.
In an attempt to understand this question, I ask you to participate in this survey which will take approximately 15-20 minutes of your time. To participate in this study, you must be 18 years of age or older, have owned a companion animal (cat, dog and/or horse) and/or have worked in the animal or human health industry within the United States. This survey is completely voluntary. You may chose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. Please note that internet communications are insecure and there is a limit to the confidentiality that can be guaranteed due to the technology itself. Your personal information however will not be stored by this tool.
The results of this study may be published only in summary form and will not include your name or any personal information. Internet communications are insecure and there is a limit to the confidentiality that can be guaranteed due to the technology itself. However, once the materials are received by the researcher, standard confidentiality procedures will be employed. The data will be stored for two years in order to analyze and provide the results for the study. If you chose to stop participating at any time, for any reason, any information that you provide will be deleted/destroyed and will not be used in the analysis of this study. If you would like a copy of this form, or a copy of your submitted data, please contact the researcher and a copy will be provided to you.

By clicking the button below, you are agreeing to participate in the study.

○ I agree to participate in the study

○ I do not agree to participate in the study

0% 100%

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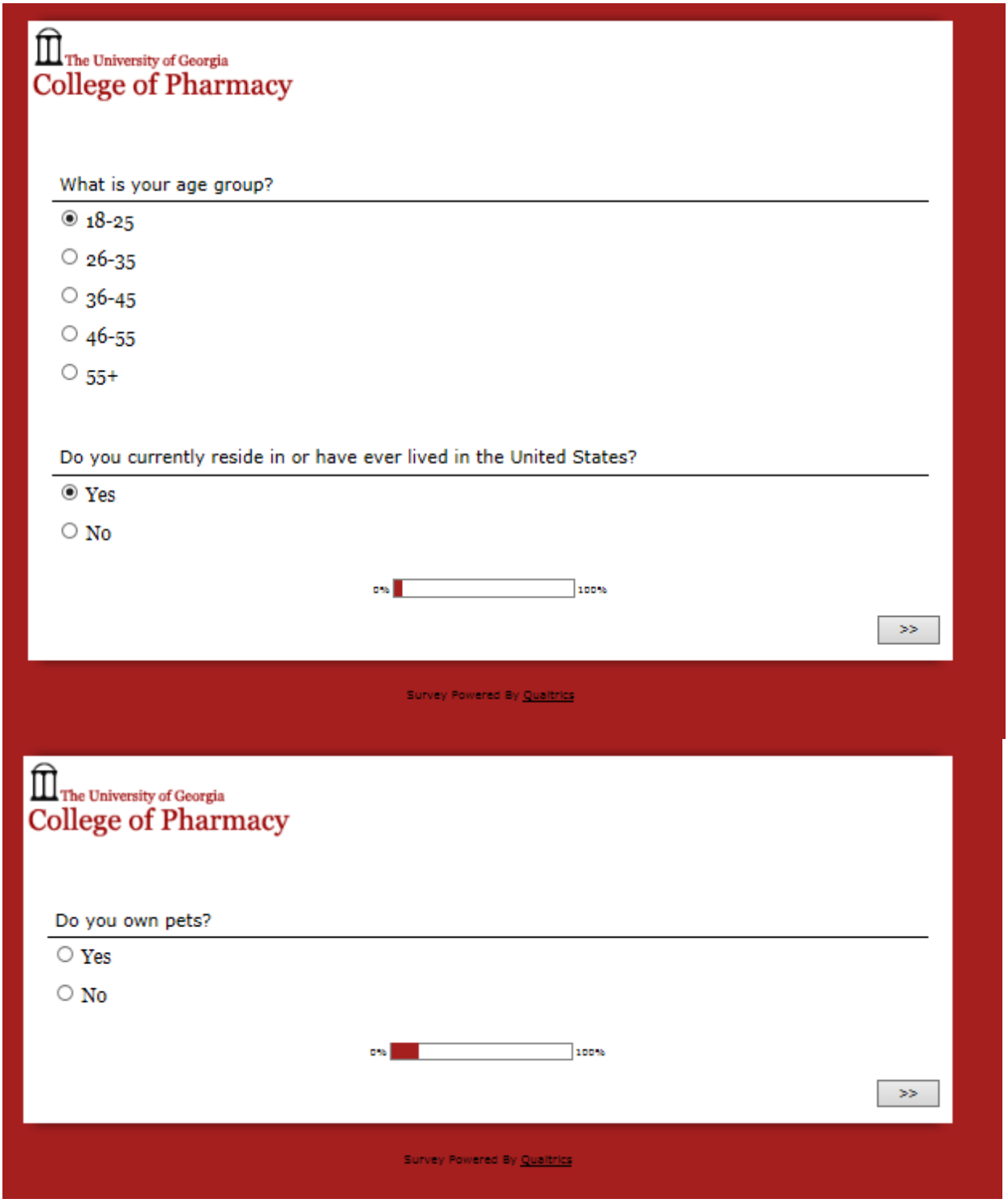
Survey Powered By Qualtrics


The University of Georgia
College of Pharmacy
What is your age group?
18-25
26-35
36-45
46-55
55+
Do you currently reside in or have ever lived in the United States?
Yes
No
0%
100%
>>
Survey Powered By Qualtrics
The University of Georgia
College of Pharmacy
Do you own pets?
Yes
No
0%
100%
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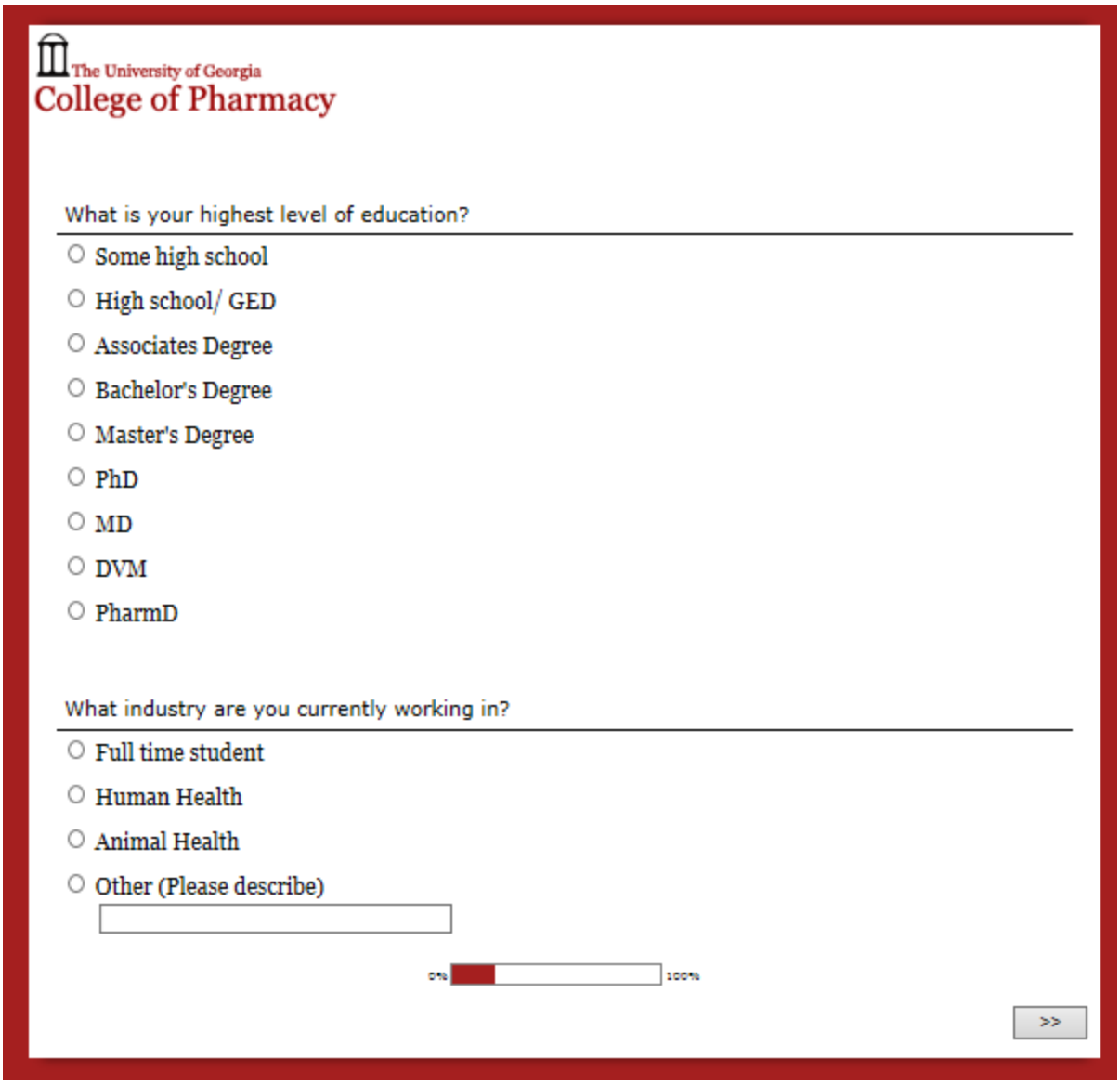
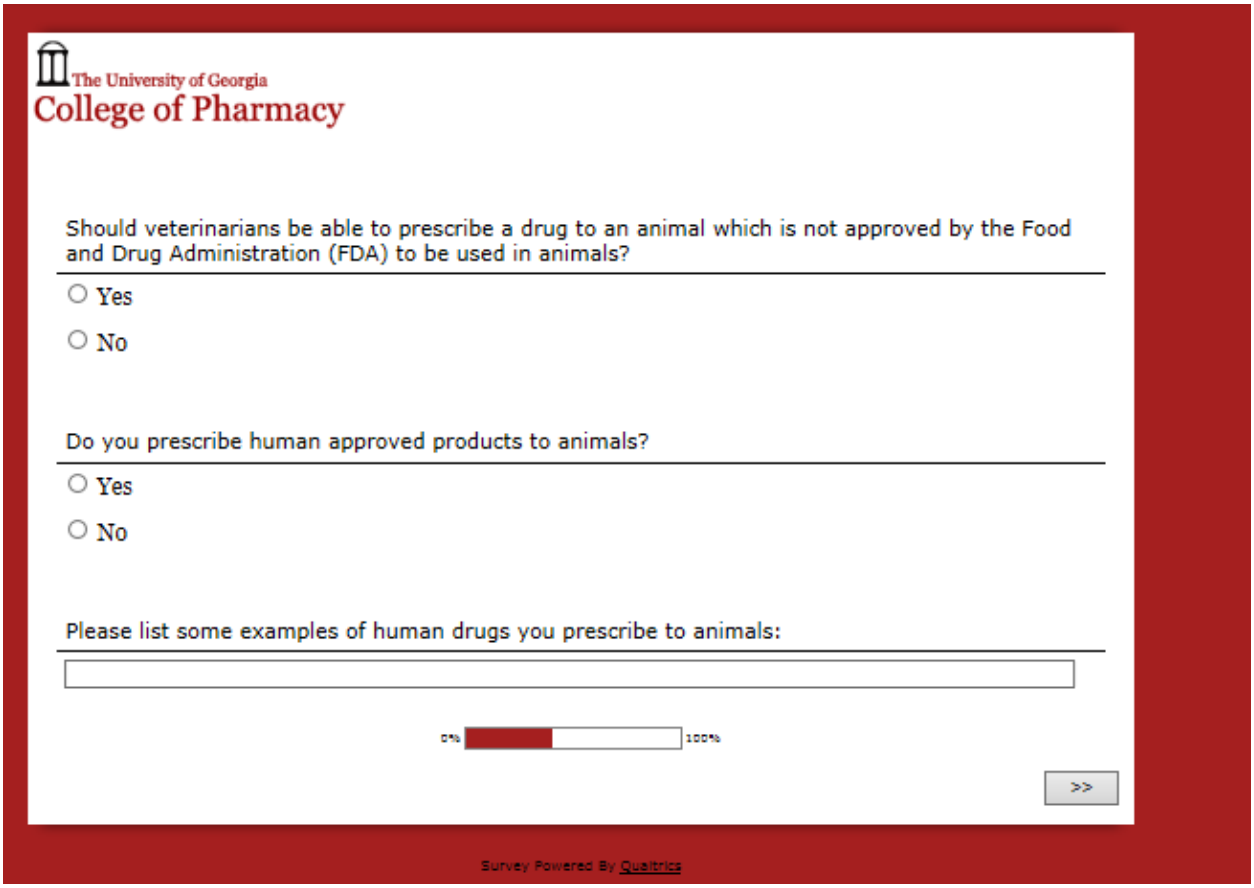
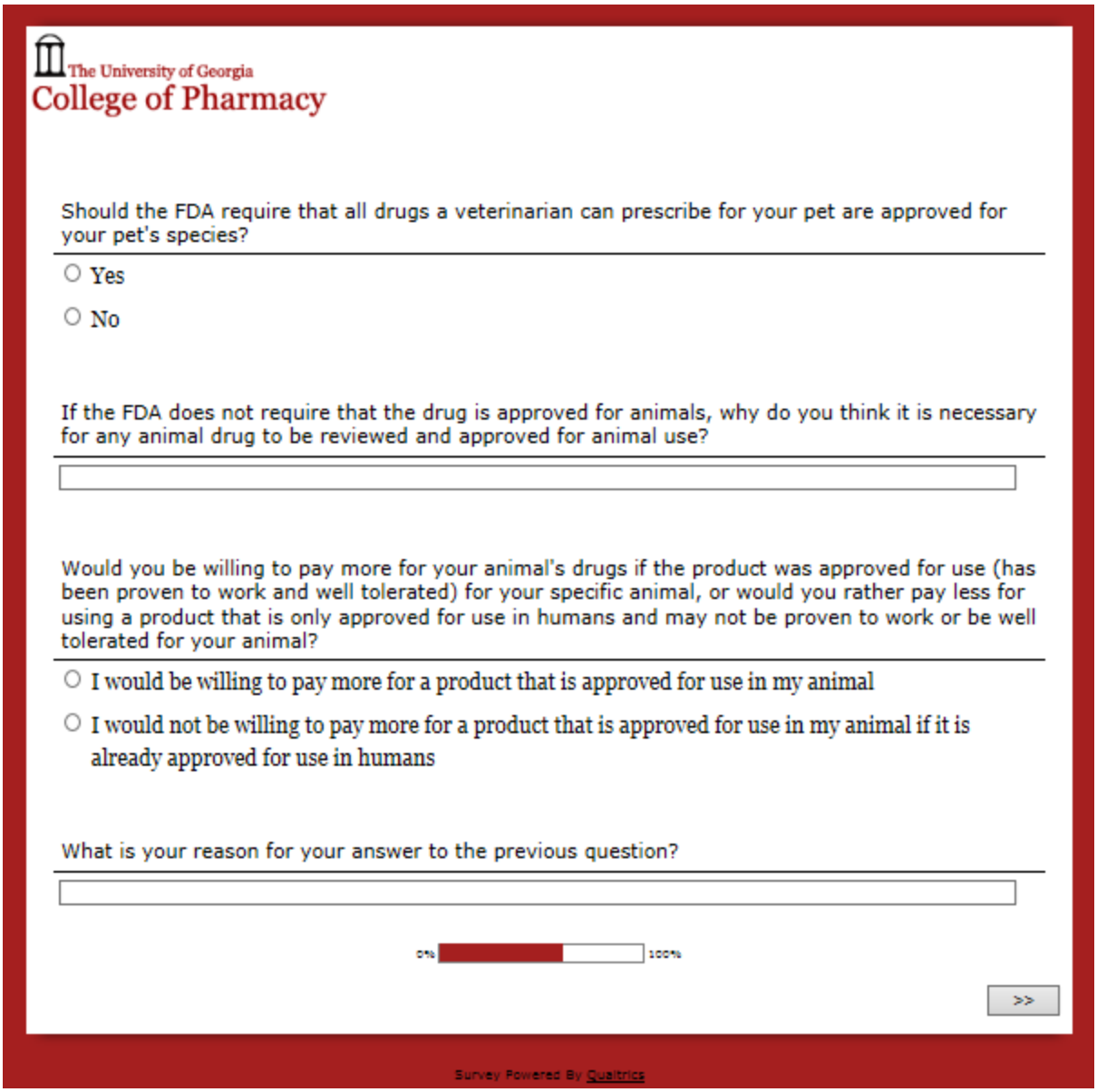

The University of Georgia
College of Pharmacy
What is your highest level of education?
Some high school
High school/ GED
Associates Degree
Bachelor's Degree
Master's Degree
PhD
MD
DVM
PharmD
What industry are you currently working in?
Full time student
Human Health
Animal Health
Other (Please describe)
0%
100%
>>


The University of Georgia
College of Pharmacy
Should veterinarians be able to prescribe a drug to an animal which is not approved by the Food and Drug Administration (FDA) to be used in animals?
Yes
No
Do you prescribe human approved products to animals?
Yes
No
Please list some examples of human drugs you prescribe to animals:
0%
100%
>>
Survey Powered By Qualtrics


The University of Georgia
College of Pharmacy

Should the FDA require that all drugs a veterinarian can prescribe for your pet are approved for your pet's species?

- Yes
- No

If the FDA does not require that the drug is approved for animals, why do you think it is necessary for any animal drug to be reviewed and approved for animal use?

Would you be willing to pay more for your animal's drugs if the product was approved for use (has been proven to work and well tolerated) for your specific animal, or would you rather pay less for using a product that is only approved for use in humans and may not be proven to work or be well tolerated for your animal?

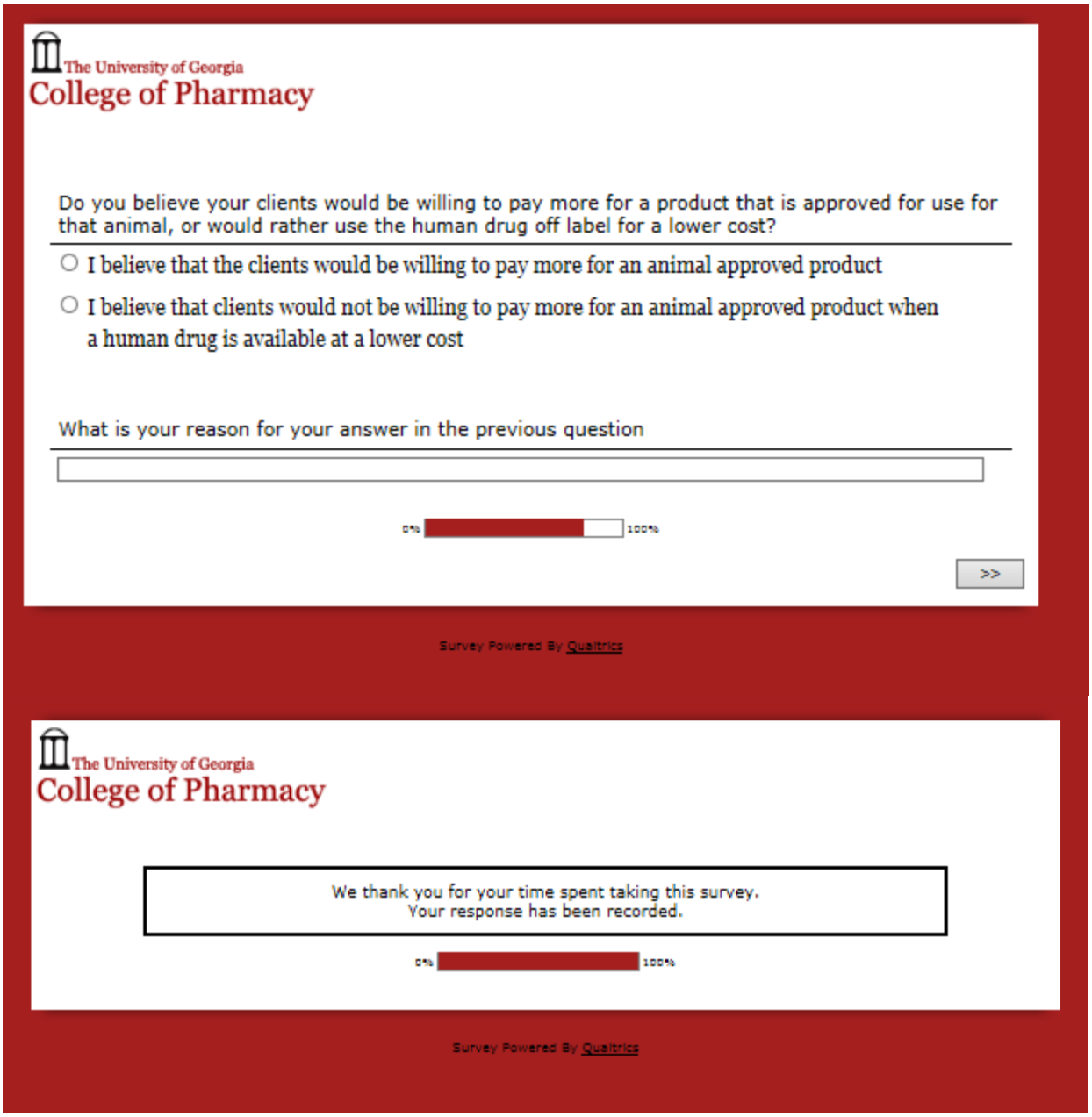
- I would be willing to pay more for a product that is approved for use in my animal
- I would not be willing to pay more for a product that is approved for use in my animal if it is already approved for use in humans

What is your reason for your answer to the previous question?

0% 100%

>>

Survey Powered By Qualtrics


The University of Georgia
College of Pharmacy
Do you believe your clients would be willing to pay more for a product that is approved for use for that animal, or would rather use the human drug off label for a lower cost?
I believe that the clients would be willing to pay more for an animal approved product
I believe that clients would not be willing to pay more for an animal approved product when a human drug is available at a lower cost
What is your reason for your answer in the previous question
0%
100%
>>
Survey Powered By Qualtrics
The University of Georgia
College of Pharmacy
We thank you for your time spent taking this survey.
Your response has been recorded.
0%
100%
Survey Powered By Qualtrics

Appendix 2: General Interview Questions

General interview questions are provided below. However depending on participant's responses, or background, additional questions may be asked.

1. Do you own pets?
2. (Question will only be asked if answered yes to question 1) What type of pets do you own?
3. (Question will only be asked if answered yes to question 1) How many companion animals (cats, dogs, horses) do you own at this time?
4. What is your highest level of education?
5. What industry are you currently working in?
6. If you have animals, are you aware if any of their medications are labeled for animal use or for human use? Please provide a list of drugs your animals are prescribed.
7. Should veterinarians be able to prescribe a drug to an animal which is not approved by the FDA to be used in animals? Why or why not?
8. (Question to only be asked of veterinarians) Do you prescribe human approved products to animals?
9. (Question only to be asked of veterinarians) Could you please list some examples of human drugs you prescribe to animals?
10. Should the FDA require that all drugs a veterinarian can prescribe for your pet are approved for the for your pet's species? Why or why not?
11. If the FDA does not require that the drug is approved for animals, why do you think it is necessary for any animal drug to be reviewed and approved for animal use?
12. Would you be willing to pay more for your animal's drugs if the product was approved for use (has been proven to work, and well tolerated) for your specific animal, or would you rather pay less for using a product that is only approved for use in humans and may not be proved to work or be well tolerated for your animal? Why or why not?
13. (Question only to be asked if participant is a veterinarian) Do you believe your clients would be willing to pay more for a product that is approved for use for that animal, or would rather use the human drug off-label for a lower cost?
14. (Question only to be asked for those working in the animal health industry) Do you think that the cost of developing and bringing a product to market with the animal approved label will be cost & time effective for the company?
15. (Question only for those working in the animal health industry) What is your reason for the answer in the previous question?

Appendix 3: Informed Consent Forms

Survey Informed Consent:

I am a graduate student at the University of Georgia, in the college of Pharmacy. I am conducting research for my graduate thesis to determine the public opinion on using human drugs off-label in companion animals (cats, dogs and horses). I am looking to understand the current public opinion to determine if the cost of developing products specifically labeled for animal health is worth the investment for the animal health industry if it is already available to be prescribed off-label by a veterinarian in the human approved drug form. The results may contribute to furthering our understanding of the animal health industry, and may help to contribute to leading the animal health industry to make more drug products specifically labeled and available to animals. There are no perceived risks associated with this research. This study has been reviewed and approved by the University of Georgia's Institutional Review board, reference number STUDY00001678.

In an attempt to understand this question, I ask you to participate in this survey which will take approximately 15-20 minutes of your time. To participate in this study, you must be 18 years of age or older, have owned a companion animal (cat, dog and/or horse) and/or have worked in the animal or human health industry within the United States. This survey is completely voluntary. You may chose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. Your personal information however will not be stored by this tool.

The results of this study may be published only in summary form and will not include your name or any personal information. Internet communications are insecure and there is a limit to the confidentiality that can be guaranteed due to the technology itself. However, once the materials are received by the researcher, standard confidentiality procedures will be employed. The data will be stored for two years in order to analyze and provide the results for the study. If you chose to stop participating at any time, for any reason, any information that you provide will be deleted/destroyed and will not be used in the analysis of this study. If you would like a copy

of this form, or a copy of your submitted data, please contact the researcher and a copy will be provided to you.

By clicking the button below, you are agreeing to participate in the study.

I agree to participate
I do not agree to participate (survey ends)

If you have any questions, please feel free to contact me either through email at pkeszler@uga.edu or by phone at 404-358-3625.

Interview Consent Form:

This is a research study to determine the public opinion on using human drugs off-label in companion animals (cats, dogs and horses). The results of this study will be used to understand the current public opinion to determine if the cost of developing products specifically labeled for animal health is worth the investment for the animal health industry if it is already available to be prescribed off-label by a veterinarian in the human approved drug form. The results may contribute to furthering our understanding of the animal health industry, and may help to contribute to leading the animal health industry to make more drug products specifically labeled and available to animals. This may also benefit you and your pets in the future to establish the best way to provide healthier pets. The title of the study is "Public Opinion of Using Human Drugs Off-Label in Companion Animal Health". To participate in this study, you must be 18 years of age or older, have owned a companion animal (cat, dog and/or horse) and/or have worked in the animal or human health industry within the United States. Your participation in this study is completely voluntary, you may choose to not participate, or withdraw from the study at any time and it will not result in penalty or loss of benefits to which you may otherwise be entitled. There are no perceived risks associated with this research. This study has been reviewed and approved by the University of Georgia's Institutional Review board, reference number STUDY00001678.

The responses that you provide will be collected and analyzed solely to answer the questions within this study. Only the researcher and principle investigator will see your data. The researcher may use quotes or summaries of your responses within the research paper. The data that is compiled from your interview will be saved with the researcher for a period of two

years following the completion of the study. This data will be stored only on the researcher's personal computer and be password protected to ensure confidentiality. After two years your data will be deleted. Only the quotes or summaries found within the final paper will be stored within the UGA library. If at any time you would like your responses be withdrawn or destroyed, you may request that the researcher destroys your responses. Your information will be destroyed and will not be used in the final research paper.

Once signing your consent form and providing it to the researcher, a time to conduct the interview will be scheduled either by phone or in person, which ever works best for your schedule and geographical location. The interview will last approximately 30 minutes to an hour and the researcher will take notes throughout the interview. Once all interviews are completed, the results will be analyzed to answer the research questions. If you wish to see the summary of your interview you may request this from the researcher.

Once signing this document, you will receive a copy for your records. If you have any questions or concerns regarding this study, please contact Patricia Keszler either by email pkeszler@uga.edu or phone at 404-358-3625.

I consent to participate in this interview for the study _____ _____
(Participant Signature) (Date)

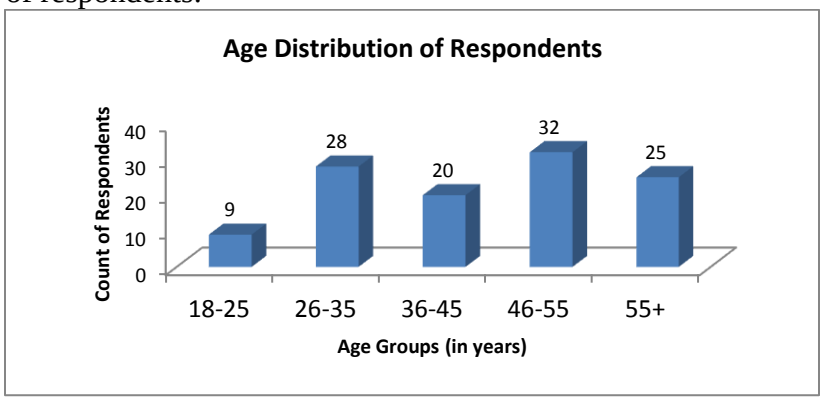
Participant Printed Name: _____
Participant Phone Number _____
Participant E-mail: _____

Researcher: Patricia Keszler
Phone 404-358-3625
E-mail: pkeszler@uga.edu
University of Georgia Graduate Student
Principle Investigator: Dr. David Mullis
Phone: 678-985-6806
E-Mail: dmullis@uga.edu
Directory Regulatory Affairs Graduate Education Program University of Georgia

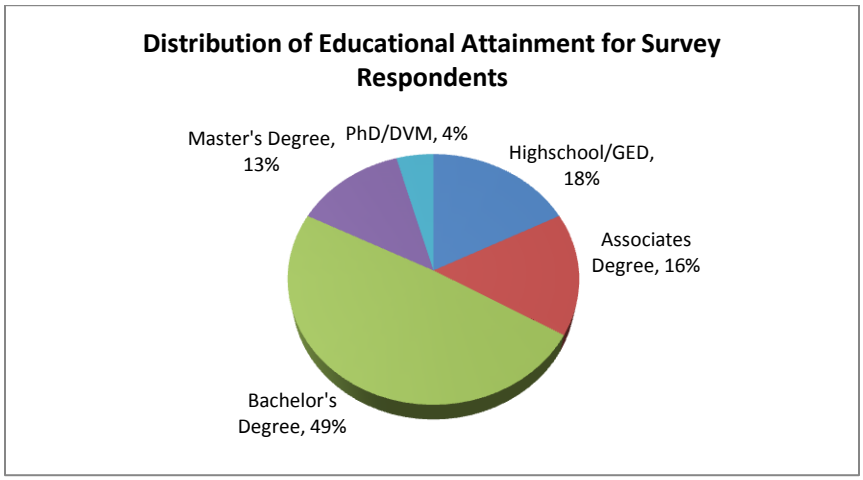
Appendix 4: Survey Reporting Tables

Survey Demographics:

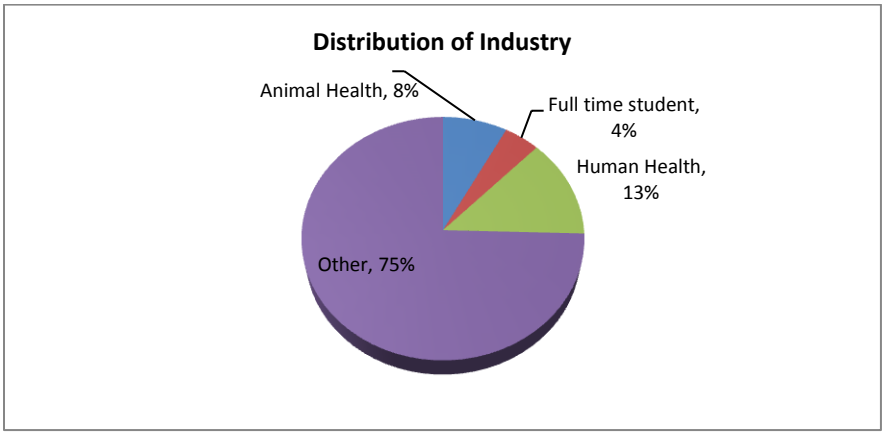
Age distribution of respondents:



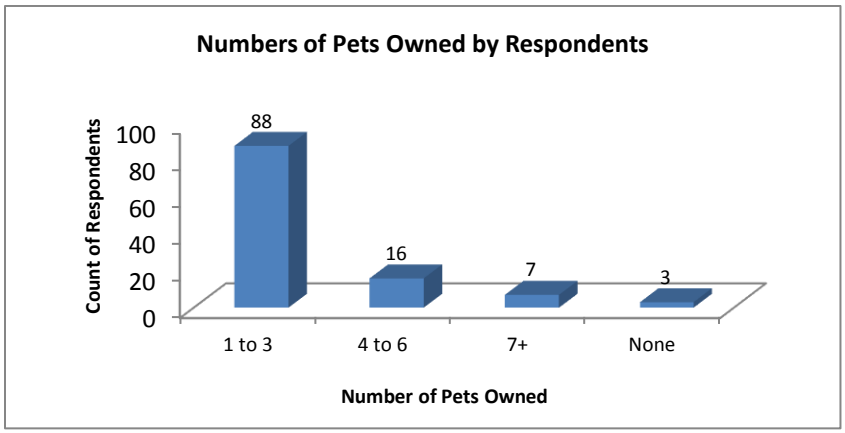
Distribution of Educational Attainment:



Distribution of Industries in which participants are employed:



Distribution of the number of pets owned by participants:



Appendix 5: Statistical Data

Demographic of Education

EDUCATION				
EDUCATION	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Associates Degree	18	15.79	18	15.79
Bachelor's Degree	56	49.12	74	64.91
DVM	1	0.88	75	65.79
High school/ GED	20	17.54	95	83.33
Master's Degree	15	13.16	110	96.49
PhD	4	3.51	114	100.00

Demographic of Age Groups

AGE				
AGE	Frequency	Percent	Cumulative Frequency	Cumulative Percent
18-25	9	7.89	9	7.89
26-35	28	24.56	37	32.46
36-45	20	17.54	57	50.00
46-55	32	28.07	89	78.07
55+	25	21.93	114	100.00

Demographic of Industry

INDUSTRY				
INDUSTRY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Animal Health	9	7.89	9	7.89
Full time student	5	4.39	14	12.28
Human Health	15	13.16	29	25.44
Other (Please describe)	85	74.56	114	100.00

Level of educational attainment vs. willingness to pay more for an animal approved drug product

Frequency:

Frequency Percent Row Pct Col Pct	Table of EDUCATION by PAY		
	PAY(PAY)		
EDUCATION(EDUCATION)	No	Yes	Total
Associates Degree	4 4.26 30.77 13.79	9 9.57 69.23 13.85	13 13.83
Bachelor's Degree	15 15.96 33.33 51.72	30 31.91 66.67 46.15	45 47.87
DVM	0 0.00 0.00 0.00	1 1.06 100.00 1.54	1 1.06
High school/ GED	5 5.32 31.25 17.24	11 11.70 68.75 16.92	16 17.02
Master's Degree	5 5.32 33.33 17.24	10 10.64 66.67 15.38	15 15.96
PhD	0 0.00 0.00 0.00	4 4.26 100.00 6.15	4 4.26
Total	29 30.85	65 69.15	94 100.00
Frequency Missing = 20			

Statistical Significance (Fisher's Exact)

Statistics for Table of EDUCATION by PAY

Statistic	DF	Value	Prob
Chi-Square	5	2.4053	0.7907
Likelihood Ratio Chi-Square	5	3.8612	0.5696
Mantel-Haenszel Chi-Square	1	0.3562	0.5506
Phi Coefficient		0.1600	
Contingency Coefficient		0.1580	
Cramer's V		0.1600	

WARNING: 58% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

Fisher's Exact Test	
Table Probability (P)	0.0022
Pr <= P	0.8955

Effective Sample Size = 94
Frequency Missing = 20

WARNING: 18% of the data are missing.

Age group vs. willingness to pay more for an animal approved drug product

Frequency:

Frequency Percent Row Pct Col Pct	Table of AGE by PAY		
	PAY(PAY)		
AGE(AGE)	No	Yes	Total
18-25	1 1.06 25.00 3.45	3 3.19 75.00 4.62	4 4.26
26-35	8 8.51 33.33 27.59	16 17.02 66.67 24.62	24 25.53
36-45	5 5.32 27.78 17.24	13 13.83 72.22 20.00	18 19.15
46-55	7 7.45 24.14 24.14	22 23.40 75.86 33.85	29 30.85
55+	8 8.51 42.11 27.59	11 11.70 57.89 16.92	19 20.21
Total	29 30.85	65 69.15	94 100.00
Frequency Missing = 20			

Statistical Significance
(Fisher's Exact)

Statistics for Table of AGE by PAY

Statistic	DF	Value	Prob
Chi-Square	4	1.9539	0.7442
Likelihood Ratio Chi-Square	4	1.9258	0.7494
Mantel-Haenszel Chi-Square	1	0.1704	0.6797
Phi Coefficient		0.1442	
Contingency Coefficient		0.1427	
Cramer's V		0.1442	

Fisher's Exact Test	
Table Probability (P)	0.0020
Pr <= P	0.7583

Effective Sample Size = 94
Frequency Missing = 20