IS THE INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS (ICCVAM) AN EFFICIENT MODEL FOR FACILITATING THE ACCEPTANCE OF ALTERNATIVE TESTING METHODS?

By

ANDREW STEPHEN WALDEN

(Under the Direction of Randall Tackett, Ph.D.)

ABSTRACT

The push for alternative testing methods that aim to greatly reduce or even replace the use of animals comes from not only a moral stance for animal welfare, but also a desire for more accurate and less expensive pre-clinical research. A federally funded committee was permanently established in 2000 to facilitate the regulatory acceptance of alternative testing methods that reduce, refine, or replace the use of animals. Its inception came with a lot of optimism and hope by those wanting to see a more modern approach to pre-clinical testing. It has been over 10 years now since ICCVAM was established. This thesis will determine the perception currently held among relevant personnel regarding its performance.

This thesis will determine if the perception of ICCVAM, in its current incarnation, is that of an efficient model for the goal of reducing, refining, or replacing current animal test methods and if so, what solutions could improve it. The tools used for this research included a questionnaire to determine the perception of respondents, along with personal interviews with key people who interact with and have great knowledge of the workings of ICCVAM.

INDEX WORDS: ICCVAM, Alternative testing methods, Animal testing

IS THE INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS (ICCVAM) AN EFFICIENT MODEL FOR FACILITATING THE ACCEPTANCE OF ALTERNATIVE TESTING METHODS?

by

ANDREW STEPHEN WALDEN

B.S., University of Georgia, 2001

A Thesis Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

MASTER OF SCIENCE

ATHENS, GA

2011

IS THE INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS (ICCVAM) AN EFFICIENT MODEL FOR FACILITATING THE ACCEPTANCE OF ALTERNATIVE TESTING METHODS?

by

ANDREW STEPHEN WALDEN

Approved:

Major Professor: Randall Tackett

Committee: David Mullis
Paul Brooks

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
August 2011

DEDICATION

This body of work is dedicated to my loving wife, Lesley, who was my motivation and my biggest supporter in completing this thesis and other degree requirements to better our soon-to-be growing family.

ACKNOWLEDGEMENTS

Thanks go to my thesis advisor, Randall Tackett, Ph. D., along with David Mullis, Ph. D., and Paul Brooks, Ph. D., for their guidance and support. A big "thank you" goes to my wife and family for their patience with me as I embarked on this most time and energy consuming endeavor. The late nights spent completing homework assignments and the shelved vacations will finally have paid off.

TABLE OF CONTENTS

TABLE OF FIGURES

Chapter 1

INTRODUCTION

Alternative Testing Methods Introduction

In the pursuit of better medicine, cosmetics, and chemicals, researchers have relied on data derived from animal testing to determine what is safe for humans. Animal testing has existed since the days of The Greeks in the Second century[1] with Aristotle being one of the earliest to have experimented with animals[2]. This has long been thought of as the best way to gauge toxicity that, in theory, would reflect a human's tolerance of the substance of interest. However, with more advancing technology that is touted as more efficient and accurate, the question has to be asked: at what point should we put forth a serious effort to reevaluate this practice? This question begs an answer not only for the sake of compassion, but for more accurate and less costly research.

The quest to reduce the number, refine the treatment, and whenever possible, replace the use of animals is a concept known as The Three R's. In 1959, zoologist William Russell and microbiologist Rex Burch conceptualized the Three R's: Replacement, Reduction, and Refinement in their book *Principles of Humane Experimental Technique*[3]. While Russell and Burch expanded on different degrees of replacement, they argued that the rational extension of replacement would result in better science[4]. In 1978, David Smyth, the late Head of the British Research Defense Society, presented a definition of "alternative" testing methods based on the Three R's principle: “All procedures which can completely replace the need for animal experiments, reduce the numbers of animals required, or diminish the amount of pain or distress suffered by animals in meeting the essential needs of man and other animals."[5] In May of 1985,

the U.S. Government mandated the consideration of the Three R's when it published the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training directive in the Federal Register. There are nine "principles" contained in the directive that dictate what is expected of anyone who tests on animals, including tests for pharmaceuticals.

The Three R's are specifically addressed in Principles III and IV of the directive as follows:

"III. The animals selected for a procedure should be of an appropriate species and quality and the minimum number required to obtain valid results. Methods such as mathematical models, computer simulation, and in vitro biological systems should be considered.

IV. Proper use of animals, including the avoidance or minimization of discomfort, distress, and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings might cause pain and distress in other animals."[6]

Reasons for Alternative Testing Methods

The desire for alternative testing methods comes from more than just a moral stance. The monetary costs, unreliable data and longer time needed, are some of the reasons beyond the moral, that people involved in drug development are pushing for these alternative testing methods[7]. Many also see alternative testing methods as "vital to improve the accuracy of preclinical testing" and to "minimize the approval of hazardous drugs and devices."[8] Many researchers find non-human model of disease expensive, inconvenient and poor predictors of human results[9]. Despite this, the number of regulated animals used for research and testing only declined from 1.2 million in fiscal year 2001 to 1.13 million in fiscal year 2009[10]. The real

numbers are actually much higher since those statistics do not take into account species of animals that are not covered by the Animal Welfare Act, such as rats and mice[11]. It is not only in the interest of animal compassion that our country should be seeking alternative testing methods, but in the interest of efficiency, safety, and accuracy as well.

So why are so many companies still so reliant on animal testing for their non-clinical data? The simple answer is that it is still required by regulatory agencies for a sufficient application and subsequent approval of a new product. However, there is also the issue of the bottom line. Even if a company wanted to develop an alternative test method that could possibly produce acceptable results for regulatory agencies, the initial costs of building the tests and validating them would be a deterrent[12].

However, the long-term benefits of implementing alternative testing methods to certain traditional methods are not lost on many as there are different groups in the United States, besides industry and government, devoted to seeking out, and even validating, alternative testing methods. Johns Hopkins University Bloomberg School of Public Health has a center exclusively devoted to discovering viable alternative testing methods, The Johns Hopkins Center for Alternatives to Animal Testing (CAAT). The Center's mission statement is "To be a leading force in the development and use of reduction, refinement, and replacement alternatives in research, testing, and education to protect and enhance the health of the public." CAAT was founded in 1981 by a $1 million grant from the Cosmetic, Toiletry, and Fragrance Association to create non-animal testing for their products[13]. Other schools such as the University of California-Davis also have similar programs.

Purpose of the Thesis

The purpose of this thesis is to determine the perception relevant personnel have about the progress made in our country's effort to curb the need for animal testing. There is a federally funded committee working on the regulatory acceptance of alternative methods called the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). This committee is composed of 15 different government agencies that work together to increase the efficiency of Federal agency test method review and to ensure alternative test methods are validated to meet acceptance standards by Federal agencies[14]. This committee was also created to coordinate efforts involving the validation, acceptance and harmonization of alternative methods in the United States. The hypothesis tested was that the majority of people surveyed would express a negative perception of the performance of the ICCVAM process. This thesis is not meant to be a criticism directed at the motivation of anyone actively working as part of ICCVAM, as this research was conducted under the premise that ICCVAM, as a committee, is committed to accomplishing the goal of reducing, refining, and replacing traditional animal test methods to the best of their ability within the rules and restrictions set forth by the government.

Chapter 2

BACKGROUND

History of ICCVAM

The actual inception of ICCVAM occurred in 1993[15]. Section 404C. (a) of the NIH Revitalization Act of 1993 called for the Director of NIH to prepare a plan that would achieve the following:

"(1) for the National Institute of Health to conduct or support research into–

(A) methods of biomedical research and experimentation that do not require the use of animals;

(B) methods of such research and experimentation that reduce the number of animals used in such research;

(C) methods of such research and experimentation that produce less pain and distress in such animals; and

(D) methods of such research and experimentation that involve the use of marine life (other than marine mammals);

(2) for establishing the validity and reliability of the method(s) described in paragraph (1);

(3) for encouraging the acceptance by the scientific community of such methods that have been found to be valid and reliable; and

(4) for training scientists in the use of such methods that have been found to be valid and reliable"[15].

To accomplish this, the Act called for The Director of NIH to establish a committee within NIH that would advise on the preparation of the plan. According to the Act, this committee was to be known as the Interagency Coordinating Committee on the Use of Animals in Research. The Act lists who should comprise the committee, including the Directors of each of the national research institutes along with representatives of agencies that the Director of NIH feels appropriate to include[15].

The committee ultimately became known as the Interagency Coordinating Committee on the Validation of Alternative Methods and in 1997, it published its final report in accordance with the Act. This report was known as the *Validation and Regulatory Acceptance of Toxicological Test Methods*[16], and still serves as one of ICCVAM's guidance documents for sponsoring entities.

It was in the ICCVAM Authorization Act of 2000 that the Director of NIEHS was instructed to "designate such committee as a permanent interagency coordinating committee of the Institute under the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods."[14] This Act also more explicitly details the purpose of ICCVAM, which is to:

> "(1) increase the efficiency and effectiveness of Federal agency test method review;
>
> (2) eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies;
>
> (3) optimize utilization of scientific expertise outside the Federal Government;
>
> (4) ensure that new and revised test methods are validated to meet the needs of Federal agencies; and
>
> (5) reduce, refine, or replace the use of animals in testing, where feasible."[14]

NICEATM

In 1998, a Center was established to administer ICCVAM called the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The other duties of this center include organizing peer review and workshops, and most importantly, conduct independent validation studies for alternative testing methods[17]. This Center is designed to work closely with ICCVAM in all aspects of its mission and will come to be discussed as one entity in many publications and reports. Dr. William Stokes, the Director of NICEATM, is also the Director of ICCVAM.

SACATM

The ICCVAM Authorization Act details the member composition of the committee, the establishment of a Scientific Advisory Committee, and the specific duties to be carried out by ICCVAM.

This scientific advisory committee was officially chartered in 2002 and became known as the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM). The purpose of SACATM is to advise ICCVAM on all relevant matters with regards to its mission of facilitating the regulatory acceptance of alternative test methods. Additionally, SACATM provides input on ways to foster partnerships and communication with interested parties. The Director of NIEHS appoints the voting members of SACATM and per the ICCVAM Authorization Act of 2000; this is to include representatives from academia, state government, industry, and animal protection organizations[18].

The declaration of ICCVAM becoming a permanent committee was met with great optimism by industry as it thought this would "give companies more certainty that regulators will

accept new testing methods that may also be less costly, less time consuming, and use fewer animals."[19] Now that over 10 years have passed, it is a perfect time to evaluate how these perceptions stand now. When ICCVAM is meeting expectations, it benefits any entity that has an interest in producing better pre-clinical data.

Nomination/Submission of Alternative Test Methods

The process by which the ICCVAM accomplishes its most important mission of making alternative test method recommendations, involves in-depth reviews of tests submitted by test method sponsors. Test method sponsors, from either industry or government, propose an alternative test method for review and recommendation by ICCVAM. Sponsors can be any ICCVAM stakeholders. Submissions or nominations consist of a request for a review of the proposed test methods, a request for ICCVAM comments on pre-validation/validation studies, or a proposal for a workshop with appropriate rationale. The test method sponsors must initiate the ICCVAM review process by bringing an alternative test method to the attention of ICCVAM[20].

There is an important difference between a submission and a nomination in the ICCVAM review process. An alternative test method submission to ICCVAM contains sufficient documentation of the test's validity prepared in accordance with ICCVAM guidelines. This means validation studies have already been performed and the test's usefulness and limitations of for a specific regulatory requirement has been documented. A nomination is somewhat of an incomplete submission. It is a proposal in need of more information. Typically, nominations are test methods for which adequate validation studies have been completed but lack a complete submission package, test methods that appear promising based on limited prevalidation or

validation data and are proposed for additional validation studies, or have pending validation studies[21].

To assure stakeholders that test information and data contained in a nomination or submission is sufficient for ICCVAM review and hopefully an endorsement, guidance documents have been created for the purpose of helping a sponsoring entity with detailing the required information and data for ICCVAM review.

Guidance Documents

The first two of these guidance documents, *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods* (ICCVAM 1997) and *Evaluation of the Validation Status of Alternative Toxicological Methods: Guidelines for Submission to ICCVAM* (ICCVAM 1999) were developed when ICCVAM was still an ad hoc committee.

Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, outlines the pathway of test method creation to regulatory acceptance into stages. More importantly, it details the criterion required by a new or revised test method before it will be considered for validation and subsequent regulatory acceptance. Ultimately, it is intended that if a sponsor carefully follows this guidance document, it should increase the chances of a proposed alternative test method of being accepted by federal agencies as producing meaningful data[20].

The second document, *Evaluation of the Validation Status of Alternative Toxicological Methods: Guidelines for Submission to ICCVAM* presents additional guidelines for sponsors for the organization of information and data necessary for an ICCVAM evaluation. Test method

performance and reliability, the current validation status of the method, and responsiveness to animal welfare issues are the three key areas of information required for a proposed test method[22].

The latest published guidance document, *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods, is the* only one created since ICCVAM was designated as a permanent committee. In addition to the guidelines and criteria included in the first two documents, there is information regarding test method nominations. This latest guidance document was written in accordance with the directive stated in the ICCVAM Authorization Act of 2000[23].

ICCVAM Review Process

Once a nomination or submission has been proposed, ICCVAM drafts a recommendation for further review activity. A level of priority on the proposed test method is also assigned.

During the initial stages of the test method review, ICCVAM collects additional pertinent data and also receives comments from the public. This review activity by ICCVAM is then commented on by SACATM during a public session. Finally, ICCVAM determines how the submitted test method will be reviewed.

At this stage, an ICCVAM working group meets with representatives from the ECVAM and JaCVAM to prepare a draft called a Background Review Document. This document will contain data and minimum procedural standards. Additionally, the working group will draft test method recommendations for uses and limitations, protocol, performance standards and any additional studies that might be needed. ICCVAM then distributes the draft Background Review

Document along with the test method recommendations to the Independent Peer Review Panel as well as making them available to the general public[20].

As stated by the ICCVAM, the goal of the Independent Peer Review Panel is "to have an international scientific composition representing the viewpoints of all interested parties in consideration of the test method". This panel holds a public meeting to receive input on the draft Background Review Document and test methods, and then prepares a report. Afterwards, the SACATM meets to comment on the draft Background Review Document, draft test method, and the Panel's report[20].

Once ICCVAM receives input from the public, the Peer Review Panel, and the SACATM, the final Background Review Document and test method recommendations can be either approved or rejected. If approved, \ the final recommendations are sent to federal agencies. It is ultimately up to the federal agencies to accept the ICCVAM recommended test methods or not[20]. For instance, if the FDA accepts a recommendation from ICCVAM for an alternative toxicology test method that reduces, refines, or replaces the traditional animal test method, then companies can use the data from this new test as part of their IND application.

While this process ensures proper oversight with essential input, it also is very time-consuming as it can take several years for the ICCVAM to approve and recommend submitted or nominated alternative test methods[24]. For alternative test methods that are reliant on emerging technology, this amount of time could actually render the test obsolete by the time it is approved.

ICATM Agreement

In 2009, a Memorandum of Cooperation was signed between ICCVAM, and similar groups in other countries. Referred to as International Cooperation on Alternative Test Methods

(ICATM), it set forth a more formal process of collaboration between ICCVAM, the European Centre for the Validation of Alternative Methods (ECVAM), the Japanese Center for the Validation of Alternative Methods (JaCVAM), Health Canada, and, as of March 2011, the Korean Center for the Validation of Alternative Methods (KoCVAM) [25]. This initiative arose due to the need for harmonization in regards to the validation and acceptance of alternative test methods between certain major global markets. This agreement aims to promote international coordination on the validation of alternative toxicity testing methods[26]. According to Marilyn Wind, who was chairman of ICCVAM at the time, this memorandum "covers three critical areas of test method evaluation: validation studies, independent scientific peer review meetings and reports, and development of test method recommendations for regulatory consideration."[26]

ECVAM

One of the groups involved with this Memorandum of Cooperation, ECVAM, was the first group to be created by a governmental body to address the need for the development of more alternative test methods that would reduce, refine, or replace certain traditional animal testing methods available. ECVAM was created in 1991 in response to a requirement laid out in Directive 86/609/EEC: "that the Commission and the Member States should actively support the development, validation and acceptance of methods that could reduce, refine or replace the use of laboratory animals."

A new directive in 2010, 2010/63/EU, provided a more detailed definition of the role of the ECVAM as:

> "a. Coordinating and promoting the development and use of alternatives to procedures including in the areas of basic and applied research and regulatory testing;

b. Coordinating the validation of alternative approaches at Union level;

c Acting as a focal point for the exchange of information on the development of alternative approaches;

d. Setting up, maintaining and managing public databases and information systems on alternative approaches and their state of development;

e. Promoting dialogue between legislators, regulators, and all relevant stakeholders, in particular, industry, biomedical scientists, consumer organizations and animal-welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches."[27]

ECVAM is considered by many to be successful in its mission with over 34 alternative testing methods that have been either developed and/or validated and are suitable for agency acceptance as of 2009. They have even validated test methods for 12 different endpoints[28]. ECVAM takes a proactive approach to seeking out traditional test methods that need to be reduced, refined, or replaced for one reason or another. One of the motivating factors for ECVAM is European legislation that has, in some cases, actually imposed deadlines for when traditional animal test methods must either be replaced[29], or reduced and/or refined[30]. This is one of a few very important distinctions between ICCVAM and ECVAM. Another is the ability of ECVAM to mandate the use of a valid and acceptable alternative test method under European law[31], which requires "that an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available."

JaCVAM, Health Canada, and KoCVAM

JaCVAM, Health Canada, and now KoCVAM are the other groups involved with the ICATM and they operate in Japan, Canada, and Korea, respectively. While all of these groups might not operate exactly the same, they all work to promote the Three R's in animal research and do so by reviewing potential alternative test methods for usefulness and suitability. JaCVAM is relatively new having been established in 2005, but has gotten off to a good start with four alternative test methods recommended and one accepted by Organisation for Economic Cooperation and Development as of 2009[32]. KoCVAM is actually the newest of these groups, established in 2009 by the Laboratory Animal Act of 2008[33].

Health Canada is a little different fromthe other groups and actually has more in common with our FDA than with ICCVAM, but in its mission of promoting good health, certainly has an interest in the implementation of alternative testing methods and the benefits that come with them[34].

Benefit to Industry

As groups such as PETA and the Humane Society push ICCVAM to further efforts to reduce, refine, and replace animal testing, it is understood that the motivation is mostly to enhance animal welfare. However, animal welfare in this country is of varying value to different individuals. It is important to understand that the introduction of alternative testing methods is of greater benefit to society than just the better treatment of animals. The benefits of alternative testing methods are many., Below are three reasons that should be of interest to any company having to currently use animal testing.

1. Accuracy

In 2003, Sharon Begley, former Science Editor at Newsweek, published an article in the Wall Street Journal about the use of animals in research titled, *Physician-Researchers Needed to Move Cures Out of the Rat's Cage*. In the article she states, "Lab mice…have responded quite well to an experimental Alzheimer's vaccine that blocked the formation of the amyloid plaques believed responsible for the disease. Lab rats with paralyzing spinal-cord injuries have walked again…after treatments. And we've cured cancer in enough rodents to fill several New York City subway systems. For people, however, there is no cure for spinal-cord injury, Alzheimer's, Parkinson's disease, multiple sclerosis, cystic fibrosis, osteoporosis, brain and other cancers…the list goes on."[35]

In 2004, it was estimated that only 8% of experimental drugs that passed the pre-clinical safety testing phase, went on to pass the human trials phase of testing[36]. Beyond this, studies of comparative drug toxicology have shown the levels of discordance between the results from animals and humans to be between 67 and 96%[37,38].

Begley's quote summarizes some of the most notable failures of animal testing, but does not offer any alternatives. However, it serves to present the notion that a lot of animal testing is in vain and that it is not so much the immediate implementation of non-animal testing, that is mostly unrealistic at this point, that we should be working on, but the proactive pursuit of seeking out alternatives.

2. Cost/Time

Animal testing is expensive. The costs associated with conducting animal research include the purchasing of the animals, the feeding, and 24 hour housing. Other costs include cages, syringes, needles, specialized surgical equipment, chemicals, stereotactic equipment, etc.,

depending on the particular experimental protocol. It is difficult to find an estimated figure of how much money is spent on animal testing here in the United States because companies are not required to disclose the number of rats, mice and birds, which are excluded from the Animal Welfare Act[39,11].

The only completely non-animal alternative testing method evaluated and recommended by ICCVAM is the In Vitro International's Corrositex assay[40]. Corrositex costs approximately $200, whereas an animal test would cost between $1,200 and $1,800. Researchers can also save up to $50,000 annually in shipping costs for a single compound with additional savings coming in the form of increased workplace safety. This test can provide a corrosivity determination in as little as three minutes to four hours, unlike animal testing that often takes two to six weeks[39].

Because animal testing is also time-consuming, these costs quickly add up to substantial amounts. According to the Humane Society of the United States, "some (animal assays) take years to complete and/or are very expensive. For example, the standard rodent bioassay for assessing carcinogenicity takes two years to conduct and costs more than a million dollars."[39] Such is the case of toxicology testing, alternative testing methods using human cells and computer-driven machines, can test thousands of chemicals at once using nothing more than a 3-by-5-inch glass tray with 1,536 wells, each a fraction of a millimeter across. Compare this with the 30 years it has taken the Environmental Protection Agency to test 2, 500 potentially toxic compounds via traditional animal testing methods[41].

Researchers are not currently required to document the number of rats, mice, and birds used in their experiments. Therefore, it is difficult to do a broad cost comparison between animal and non-animal tests. This is due to the animals mentioned being excluded from the Animal Welfare Act, which requires strict record keeping in regards to animal testing.

3. Marketing

In one opinion poll, 79% (or 4 out of 5) of respondents said they would be likely to swap to a brand of cosmetics that was not animal tested if they discovered that their existing brand was tested on animals[42]. With the fierce competition in the marketplace, any advantage is helpful. Consumers are not expected to do research regarding the pathway with which a product was approved and precisely what kind of testing was necessary along the way. A bold claim on the label that a product was not tested on animals, or that the number of animals was as minimal as is allowed, would theoretically appeal to those 79% of people and influence their buying decision. Many cosmetic companies already have these claims printed on the labeling.

Chapter 3

METHODOLOGY

Questionnaire

Initially, the research regarding the efficiency of ICCVAM was to center around comparisons to seemingly parallel groups such as ECVAM and JaCVAM. The thought was to contrast the accomplishments of ICCVAM to that of these similar groups, with the accomplishments of these groups to serve as an index.. However, there are too many variables involved in how each group conducts their work to draw accurate comparisons about ICCVAM's performance. Additionally, an overall examination of ICCVAM's accomplishments proved to be very subjective. The best way to gain an understanding of the performance of ICCVAM is to simply ask personnel who have interactions with and/or knowledge of their work. As with any federally funded entity, public perception of ICCVAM's performance is critical. The perception of job performance reflects how that performance satisfies the expectations of the people who stand to benefit from the ICCVAM process. The perception of those who are most familiar with ICCVAM provides an idea of how well they are doing the job that is expected of them. Prior research on the attitudes and opinions towards ICCVAM was nonexistent. Therefore, this initial research determined the perception regarding ICCVAM's performance. One of the most reliable ways to measure public perception is through the use of surveys[43] so that is what was used, along with personal interviews, to collect the necessary data for this research. Questionnaires and surveys have been used previously to accurately capture the opinions of a sample population regarding the performance of other groups such as the FDA[44], and even the United States government as a whole[45].

The most commonly used question format for assessing participants' opinions[46] on a questionnaire is the Likert-type scale. This is due to the fact that it is simple to create and it is easy for a potential respondent to understand and complete. The Likert Scale was developed by Rensis Likert in 1932. It is designed to measure a respondent's level of agreement with a specific statement. For the questionnaire, there was a five-point scale; Strongly Disagree, Disagree, No Opinion, Agree, and Strongly Agree. A value is assigned to each response and the total score is obtained by adding the values for each response.

While some may argue that omitting a neutral response option such as "No Opinion", forces respondents to make a definitive choice on which way they lean on an issue[47], and encourage choice[48], it was not appropriate for this research. All respondents needed to be very comfortable with their choices on this survey as there was no room for them to elaborate. Also, answering "No Opinion" in regards to some of the statements denotes an attitude that can be viewed as negative because the role of ICCVAM is supposed to be beneficial to qualified respondents. If respondents do not feel a positive sentiment toward ICCVAM, then the committee could be viewed as being somewhat ineffective or a waste of resources.

In his book, *Beginning Research in Psychology*, Colin Dyer, states that "'attitude scales do not need to be factually accurate – they simply need to reflect one possible perception of the truth. …[respondents] will not be assessing the factual accuracy of each item, but will be responding to the feelings which the statement triggers in them."[49] It is this perception of the truth that will give the best indication of the performance of ICCVAM.

This survey was kept relatively short with only 7 questions because it has been proven that there is a significant increase in the percentage of incomplete surveys as more questions are added for surveys between 1-15 questions. This increase per question lessens with each

subsequent question for surveys that have greater than 15 questions[50].

The questions were phrased in a way as to not lead a respondent. No questions were prefaced with any information that would help respondents form an opinion. This questionnaire was designed to gauge their opinion on the statement based on current knowledge of the performance of ICCVAM. As stated, the respondents were simply asked to give their level of agreement with a short statement regarding ICCVAM.

The questionnaire was designed to produce appropriate ordinal data that could be ranked according to strength of opinion. The intention was to recognize stronger feelings towards the statement and rank it as such.

The answers were graded as follows:

Strongly Disagree – 5 points

Disagree – 4 points

No Opinion – 3 points

Agree – 2 points

Strongly Agree – 1 Point

The weight applied to each answer was chosen to reflect its value in supporting the hypothesis. An answer of "No Opinion" carries a value because in regards to this thesis, a neutral attitude toward ICCVAM by a respondent with interests in the process of drug development, and particularly research, should be viewed as a negative response. If ICCVAM is receiving federal funds, it should be looked upon as a favorable endeavor. The respective value of each answer was multiplied by the number of respondents who chose such, then divided by the total number of respondents. A mean greater than 3, which would indicate the average respondent has a negative perception of the performance by ICCVAM, would be supportive of the hypothesis that

the perception among people familiar with the ICCVAM is that it is not meetings its performance expectations. With five answer choices for the Likert-type questionnaire, it was determined that calculating the mean would yield the most significant data as opposed to calculating the mode. Relying on the mode as being the determinant is not appropriate because while this would indicate the most popular response it would also skew the true sentiments of the respondents. For example, 9 respondents might "agree" with a statement while only 6 "strongly disagree" and 5 "disagree". It is the mean that gives us a better representation of the perceptions of the sample population.

PERSONAL INTERVIEWS

For this research a mixed-method approach was used utilizing both questionnaires and personal interviews. This combination of quantitative and qualitative methods gives the advantage of obtaining more descriptive results than those from the questionnaire alone while also giving a more complete understanding of the viewpoints of the subjects. However, the disadvantages include the fact that it is more time-consuming and the data from both methods can be difficult to link together[51].

Personal interviews were conducted with relevant individuals for the purpose of acquiring perspectives from those who work, or have worked in the past, with the ICCVAM in some capacity. Personal interviews were invaluable to my research because of the opportunity to question statements as they were received. Since there has not been any extensive prior research done on this topic of sentiment toward the performance of ICCVAM, it was important to lay the groundwork for future research by identifying areas of the ICCVAM process that were consistently lamented by the interviewees. These personal interviews were also conducted to

address the limitations of the questionnaires. The information given by the responses to the surveys was restricted by the five answer choices. In personal interviews, the respondent had a chance to expand on their answers and was free to provide information they felt was relevant to the question. Information from surveys provides an idea as to the feelings individuals have toward the performance of ICCVAM, but personal interviews gave better insight into why they might feel that way.

Choosing the individuals to be interviewed involved researching their background and their level of involvement with ICCVAM. The inclusion criteria for the subject population included working, in some capacity, with pre-clinical research, and must be knowledgeable about the workings of ICCVAM. This could include any of the following:

- Members of the medical products industry
- Lab workers involved in preclinical research
- Representative of academic centers working to develop alternative methods (Johns Hopkins University Center for Alternatives to Animal Testing, UC Davis Center for Animal Alternatives Information, etc...)
- Representative of an Animal Welfare Group (PETA, Physicians Committee for Responsible Medicine, etc...)
- Representative of ICCVAM

Unlike the quantitative data collected from the questionnaire, personal interviews yielded qualitative information that will have to be coded to be more readily measured. For this purpose, a constant comparative method was used to analyze the interview data. This method allows for the identification of consistent codes in the collected information with which to produce a substantive theory about the perceptions held by the interviewees[52]. Additionally, this method

allows for flexibility as it does not require the use of any particular unit of analysis[53]. This strategy also allowed for the recognition of recurring topics that were the cause of attitudes expressed towards the performance of ICCVAM.

Each personal interview was recorded and subsequently transcribed where a general inductive approach[54] was used to analyze the interview data. The answers to each interview question were coded thereby allowing for accurate analysis through the comparison of attitudes and themes between all answers given for that particular question. The analysis of the transcribed data included line by line comparisons of answers that entailed identifying synonymous key words used by the interviewees to express their feelings towards the subject of each question. Eventually the answers were deconstructed to a point where it was plausible to make an accurate classification of their answer as “Yes”, or “No” to the respective question. When it became clear that certain themes were emerging from the answers of all interviewees, those themes were identified as well and were used for the topics of further discussion.

Chapter 4

IMPLEMENTATION

E-mail

The Likert-Type Interval Scale questionnaires were emailed to individuals identified as possibly having an understanding and/or involvement with pre-clinical research along with some knowledge of the role and function of ICCVAM. To gather these e-mail addresses, different resources were used including the following:

- Industry referrals
- ASPET (American Society for Pharmacology and Experimental Therapeutics) Member Directory)
- Contact information listed on respective academia/laboratory websites for faculty and staff such as Johns Hopkins University Center for Alternatives to Animal Testing, Stanford Research Animal Facility, Utah State Animal Lab, and UC Davis Center for Animal Alternatives Information
- Staff contact information of pre-clinical research service companies listed on The National Biotech Register, available at http://www.biotech-register.com/biotech-directory/PPCN.cfm

The service used to send out the questionnaires to subjects was Survey Monkey. Using this service gave the ability to track which e-mail addresses completed the questionnaires, along with their respective answers, as well as how many questionnaires were not delivered to specified addresses for whatever reason.

Respondents who answered "Yes" to statements #1 (I have an interest and/or remedial knowledge of pre-clinical (non-human) research testing) and #2 (I am familiar with the role and function of the Interagency Coordinating Committee on the Validation of Alternative Methods) were placed into one of four categories; academia, industry, animal welfare groups, and those who responded to the questionnaire via one of the two web links posted on the internet as previously explained. The Academia category included any respondent employed by and/or affiliated with an educational institution such as a university research laboratory. Industry respondents were those employed by any for-profit company. This could include pharmaceutical companies or contract research organizations. The third category, Animal Welfare, included anyone affiliated with groups such as PETA, the American Anti-Vivisection Society (AAVS), or the Physicians Committee for Responsible Medicine (PCRM). While some people may view members of these organizations as holding extreme views on the subject of animal testing, it was important to include them as these groups actually had input in the creation of ICCVAM and helped set its course in 2000, when it became a permanent committee. Additionally, members of animal welfare organizations such as PETA are also required by law (ICCVAM Authorization Act of 2000) to be included in the membership of SACATM, which is charged with providing advice to ICCVAM.

Web link

The fourth group included respondents who completed the questionnaire in response to seeing a link directing them to it. This open web link was posted on the AltTox.org's internet forum, as well as on the Regulatory Affairs Professional Society's message board on LinkedIn.com (LinkedIn.com is a professional, social networking site). These locations were

identified as being websites that were visited by the target population of this research. Both of these Internet locations require an approved membership for anyone to participate in a discussion conducted on the respective site. The memberships involve screening by site administrators to ensure potential members are involved, in some way, with the focus of the site. Since this web link was only posted on two restricted Internet sites that require members to have an interest in regulatory affairs and/or pre-clinical research testing, it is safe to assume these anonymous individuals will give valuable data for this thesis. Additionally, the answers given by these respondents were compared to all the answers given by people who responded to e-mail invitations to assure there was no one who completed the questionnaire a second time through the web link.

Gathering data from these four demographic groups ensured that the data collected is accurate for a good cross-section of those with knowledge about the activities of ICCVAM and will be most meaningful.

Phone

The personal interviews were conducted over the phone and were scheduled for a time, which was convenient for the interviewee. The approach used in the interviews was one of a standardized, open-ended style, which allows the interviewees to fully express themselves, but does make it more difficult to chart responses. The questions asked in the interviews were constructed based on the statements contained on the questionnaires, but were not as specific. The more general interview questions were to encourage expansive answers by the interviewees. Interview questions were not piloted due to the lack of a representative sample available for use, however during each interview the interviewee was asked to state if they did not understand the

question. Additionally, if an interviewee seemed to give an answer that indicated a lack of understanding as to what the question was asking, then a clarification would have been given. The following questions were asked of every interviewee, except Dr. William Stokes. The questions were as follows:

1. How familiar are you with ICCVAM?

2. What are your impressions of the job being done by ICCVAM?

3. Do you feel ICCVAM is inefficient?

4. If so, what are some ways you think ICCVAM might more efficiently accomplish its objective?

5. Do you feel ICCVAM should be given more power by the government to accomplish its objective?

The audio of each interview was recorded for accuracy and to more easily reference for data analysis. In the interest of space, the entire transcript of each interview will not be reproduced here. However, relevant quotes will be used for discussion.

The following individuals were interviewed:

Jessica Sandler
Regulatory Testing Division
PETA

Chad Sandusky
Director of Research and Senior Toxicology Advisor
Physicians Committee for Responsible Medicine

Paul A. Locke, MPH, DrPH
Associate Professor
Director, DrPH Program in Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health

Anonymous #1
Heavily Involved in Animal Research Issues

Anonymous #2
Heavily involved in Animal Research issues
Former SACATM Working Group Member

Catherine Willett, Ph.D.
Science Policy Advisor
PETA

William Stokes, DVM
Executive Director
ICCVAM and NICEATM

During the interview of Dr. Stokes, the questions varied slightly as to avoid obvious and time-wasting answers. For example, Dr. Stokes was not asked how familiar he was with ICCVAM. He was also not asked if he felt ICCVAM was inefficient, instead he was asked what he thought were some areas that ICCVAM need improvement.

Each potential interviewee was forwarded an IRB approved letter stating the purpose of the research and what their involvement would entail. Additionally, the potential interviewees were told in the letter that the interview would be recorded for accuracy and that they had the option of remaining anonymous if they so wished.

The interaction with human subjects classifies this study as human research. The conduct of this study, including all activities related to it, was reviewed and approved by The University of Georgia's Institutional Review Board on April 17, 2011. It was assigned Project Number 2011-10759-0.

Chapter 5

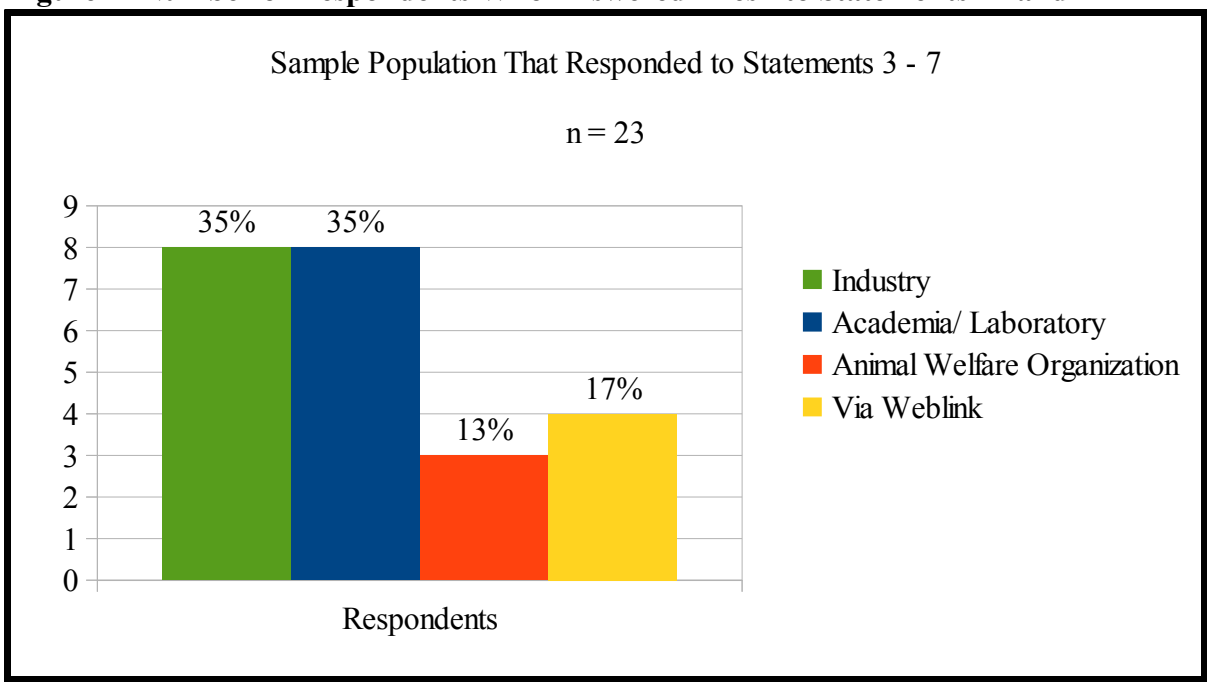
RESULTS

Questionnaire Data

In total, 500 e-mail invitations were sent out with a link to the questionnaire. If someone did not respond to the first e-mail invitation, then a second invitation was sent two weeks later. In a time frame of two months, 42 people responded to the e-mail invitations, or Internet link, and completed the questionnaire. It must be recognized that sending questionnaires via e-mail presents inherent problems that affect the ratio of respondents to total recipients. The Survey Monkey service does not show how many questionnaire e-mails were actually opened and/or viewed. Survey Monkey is a nationally known survey service that makes it very susceptible to be labeled as "junk" or "spam" by many e-mail service providers. There is no way to determine how many people actually received the questionnaire. The advantages of Survey Monkey outweigh its disadvantages by streamlining the process of e-mailing a large group of people, producing easy to analyze results, and keeping a record of each respondent's information, among others. Being able to trace each respondent's e-mail address allowed for positive demographic classification of the respondents.

Figure 1 illustrates the distribution of only those respondents who answered affirmatively for both statement #1 (I have an interest and/or remedial knowledge of pre-clinical (non-human) research testing*),* and statement #2 (I am familiar with the role and function of the Interagency Coordinating Committee on the Validation of Alternative Methods).

Figure 1- Number of Respondents Who Answered "Yes" to Statements #1 and #2



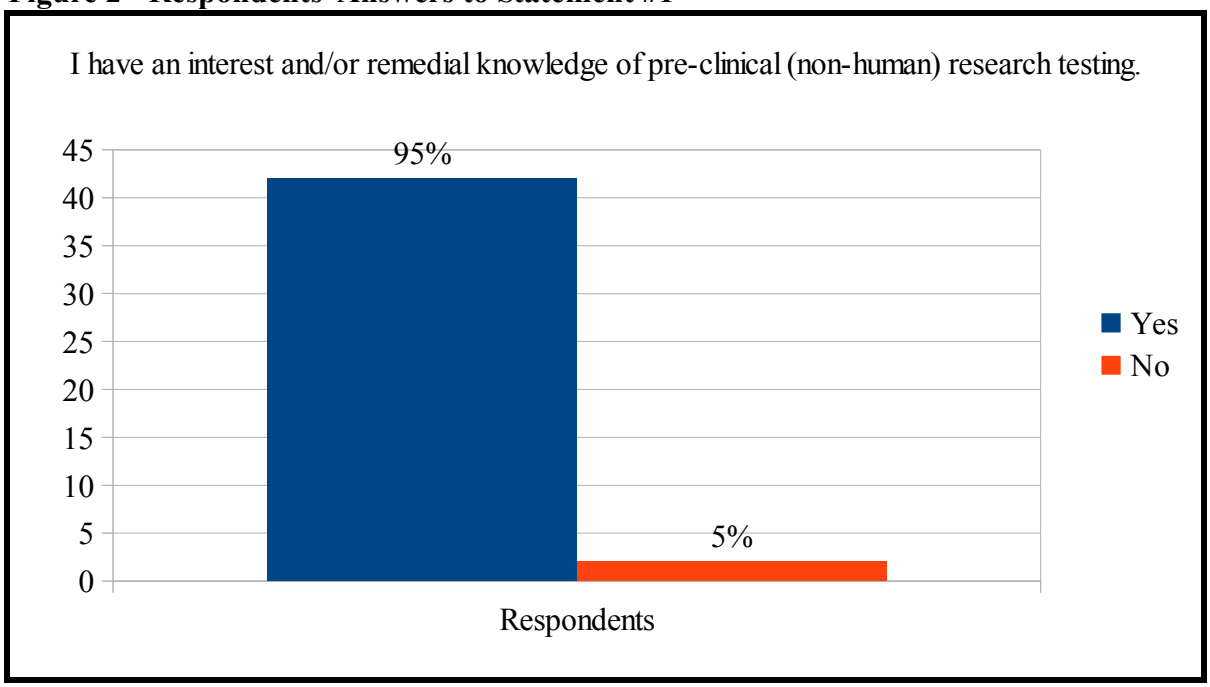
On the following pages, each statement is presented exactly as it appeared on the questionnaires given to the sample population along with graphs that depict how respondents answered. The results for statements 3 through 7, which are the five-level Likert items, are displayed with two graphs for each question. One graph shows the basic results of the given answers along with a second graph that further breaks down how each demographic answered. This breakdown revealed any trends in respect to certain groups. Additionally, the data is strengthened when proven to come from a cross-section of respondents.

<u>Statement 1</u>: I have an interest and/or remedial knowledge of pre-clinical (non-human) research testing.

This is the first of two qualifying questions meant to filter out responses that are not of value for this thesis. The target population was those who are involved and/or has an interest in pre-clinical research. If the questionnaire was sent to someone that did not meet this inclusion

criterion, then their response of "no" would be notification of this. The results are displayed in Figure 2.

Figure 2 - Respondents' Answers to Statement #1



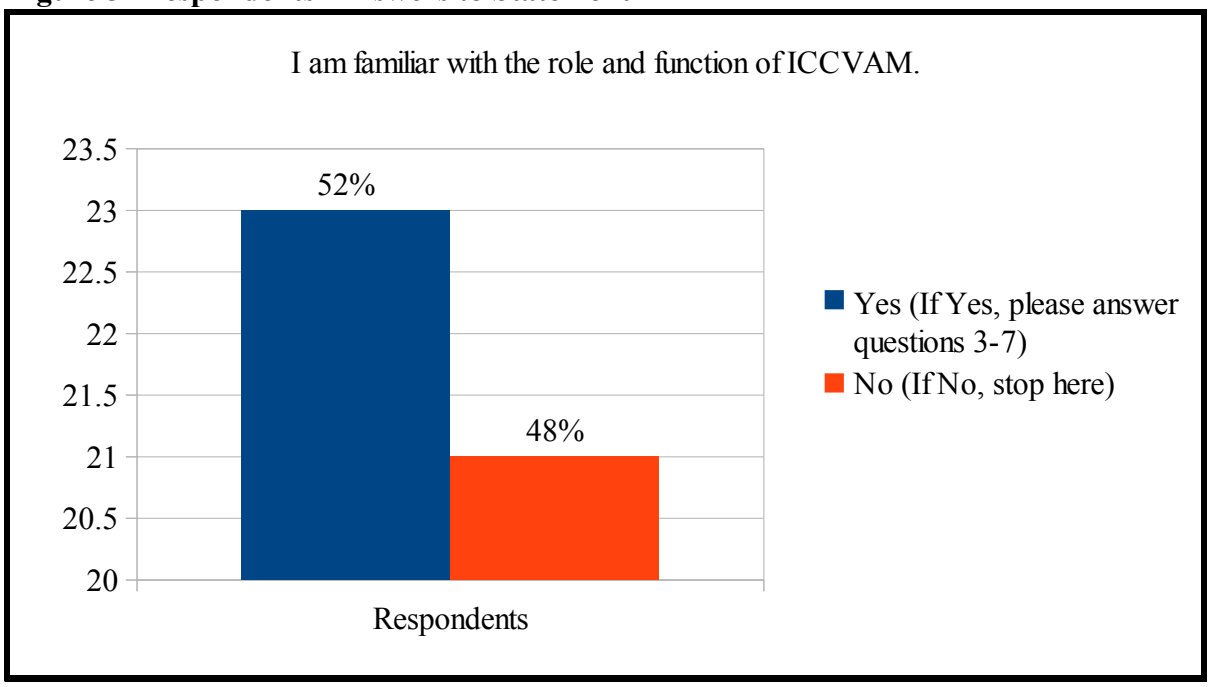
Of those surveyed, 96% of respondents had a level of interest in the field of pre-clinical research. This was a high ratio of qualified respondents, which yielded valuable data for this research.

<u>Statement 2</u>: I am familiar with the role and function of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

This is the second and final of two qualifying questions meant to filter out responses from those who are not aware of the ICCVAM. However, "No" responses to this question are of value to this thesis. When someone who is involved in and/or has an interest in pre-clinical research has no familiarity with ICCVAM, it indicates that there is a disconnect. A committee, such as

ICCVAM, that was created to benefit potential alternative test method developers and/or sponsors should make its presence known as a resource for these people.

Figure 3 -Respondents' Answers to Statement #2



While this is a qualifying question for the next five questions, it provided important data pertaining to ICCVAM awareness. Looking at the Figure 3, 52% of the respondents were familiar with the work of ICCVAM. However, 55% of the 42 respondents who stated that they had an interest and/or involvement with pre-clinical research were familiar with the work ICCVAM does.

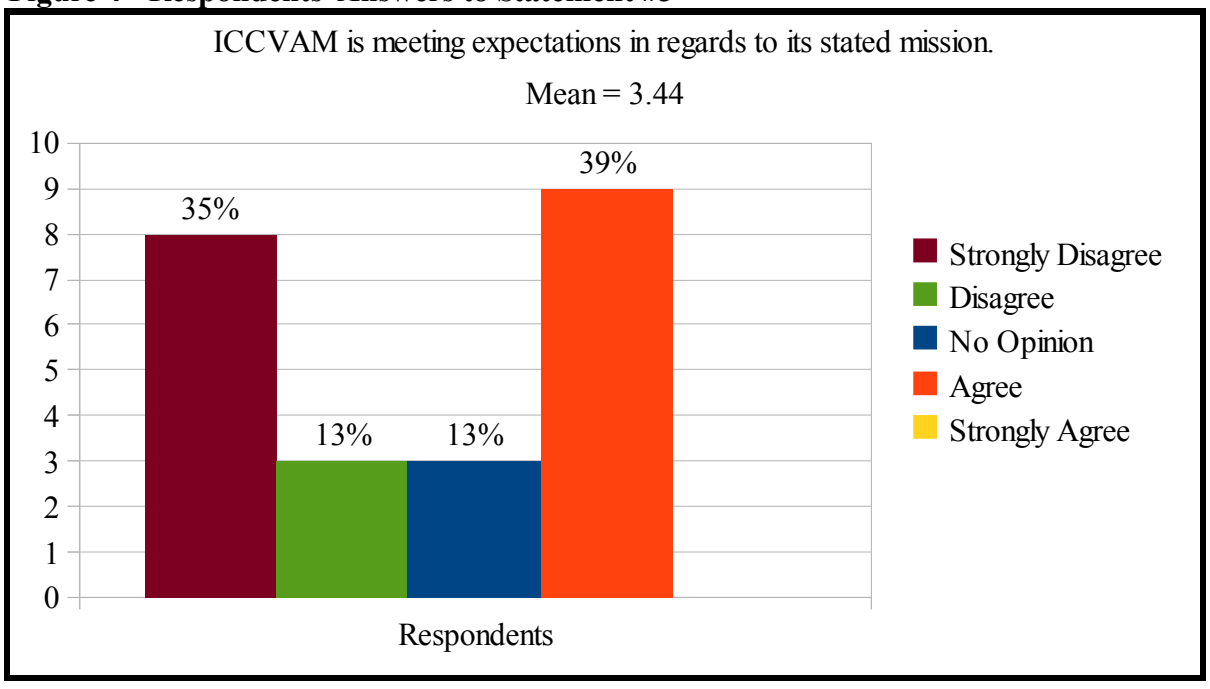
Supporting this survey finding was a telling reply from a new agency representative for ICCVAM whom a personal interview was requested for this thesis. This person's reply was that she was not knowledgeable enough about ICCVAM to comply with such a request. It was very surprising to learn how little about ICCVAM this freshmen representative knew.

<u>Statement 3</u>: ICCVAM is meeting expectations in regards to its stated mission.

The ICCVAM mission statement is, "to facilitate development, validation and regulatory acceptance of new and revised regulatory test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment." This question was designed to gauge performance of ICCVAM by those who are familiar with its intended purpose. The data collected from the answers to this statement that ICCVAM is not efficiently going about the mission of facilitating alternative test method development and acceptance, supports the hypothesis of a negative perception of ICCVAM

Those who claim to be familiar with the workings of ICCVAM understand its mission and this statement asks them only to answer whether they feel it is meeting expectations set by this mission statement. Figures 4 and 5 show the results of the responses to this statement.

Figure 4 - Respondents' Answers to Statement #3



Twenty-three respondents were eligible to reply to this statement, along with questions 4-7, after having answered affirmatively for statements #1 and #2. Twelve out of 23 respondents believe that ICCVAM is not meeting the expectations in regards to its stated mission. Additionally, 3 respondents had no opinion towards the performance of ICCVAM with only 9 respondents agreeing with the statement that ICCVAM is meeting expectations.

Again, in order not to lead anyone on this statement, it was not prefaced with statistics pertaining to ICCVAM's job performance so as to give them the information to make a more informed answer, but giving a positive or negative answer implies that a respondent is confident in the facts about ICCVAM's job performance.

Figure 5 - Answers to Statement #3 by Demographic

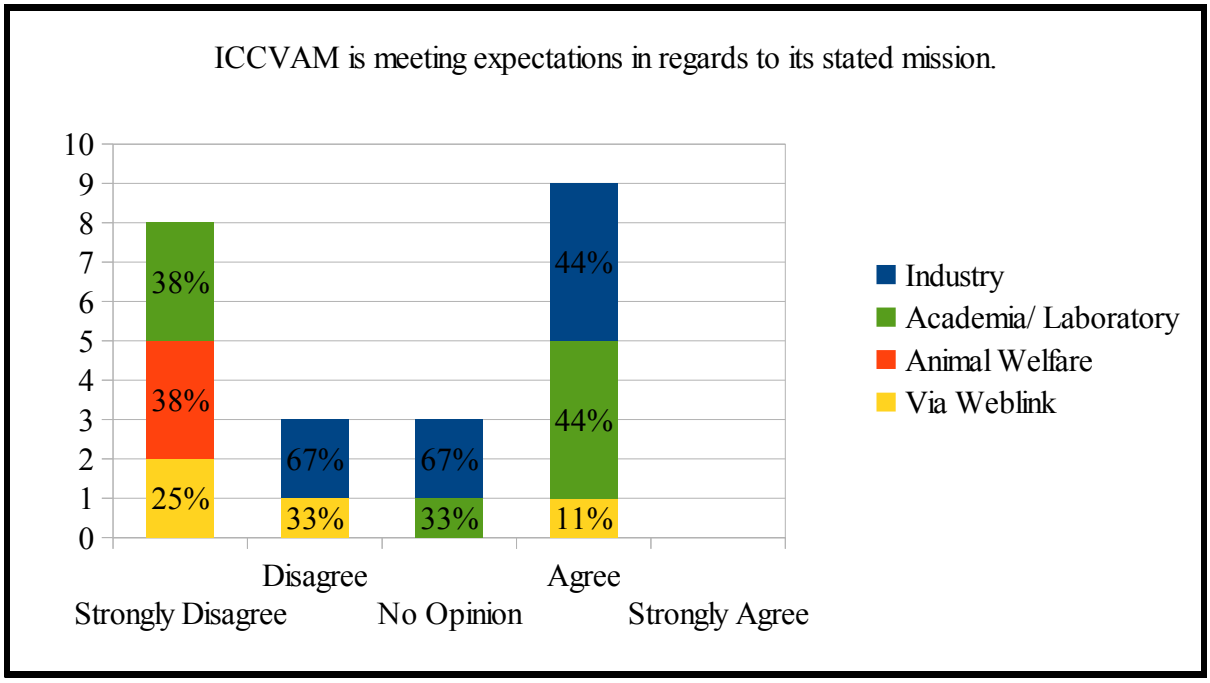
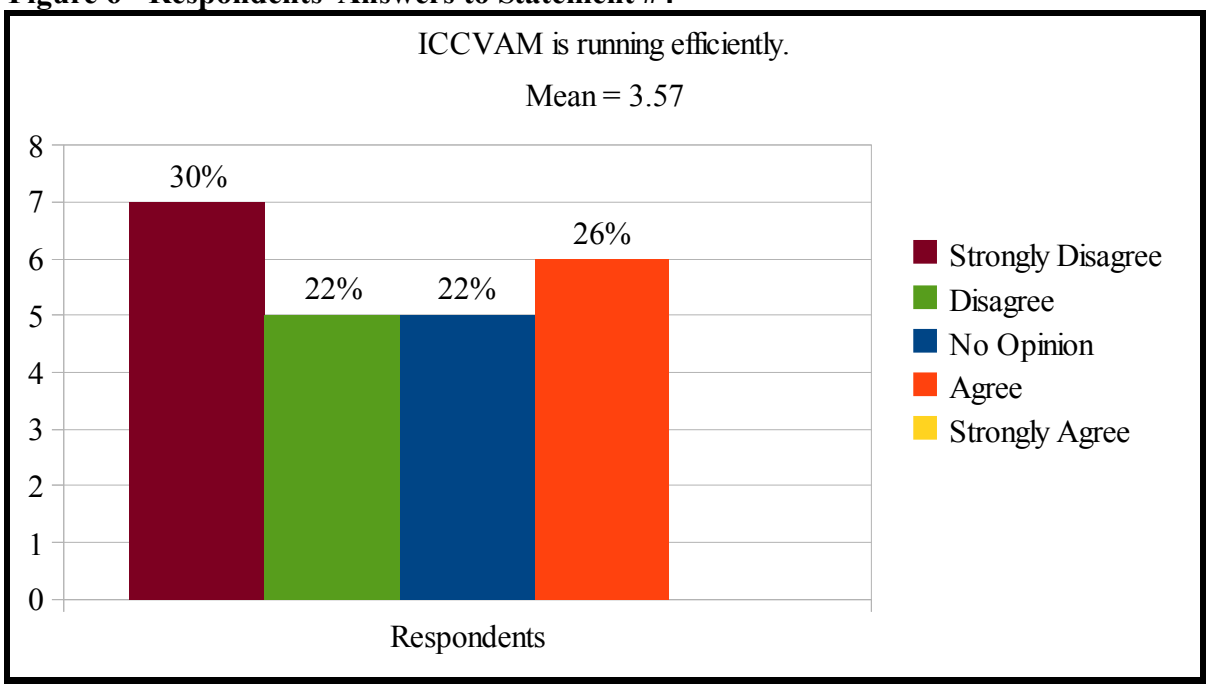


Figure 5 further breaks down the responses given for statement #3 demographically. All four demographic categories gave negative responses to this statement. This indicates a support of the hypothesis by all four demographic groups.

<u>Statement 4</u>: ICCVAM is running efficiently.

Like question 3, question 4 was intended to gauge perception of the respondents in regards to the actual job being performed by the ICCVAM.

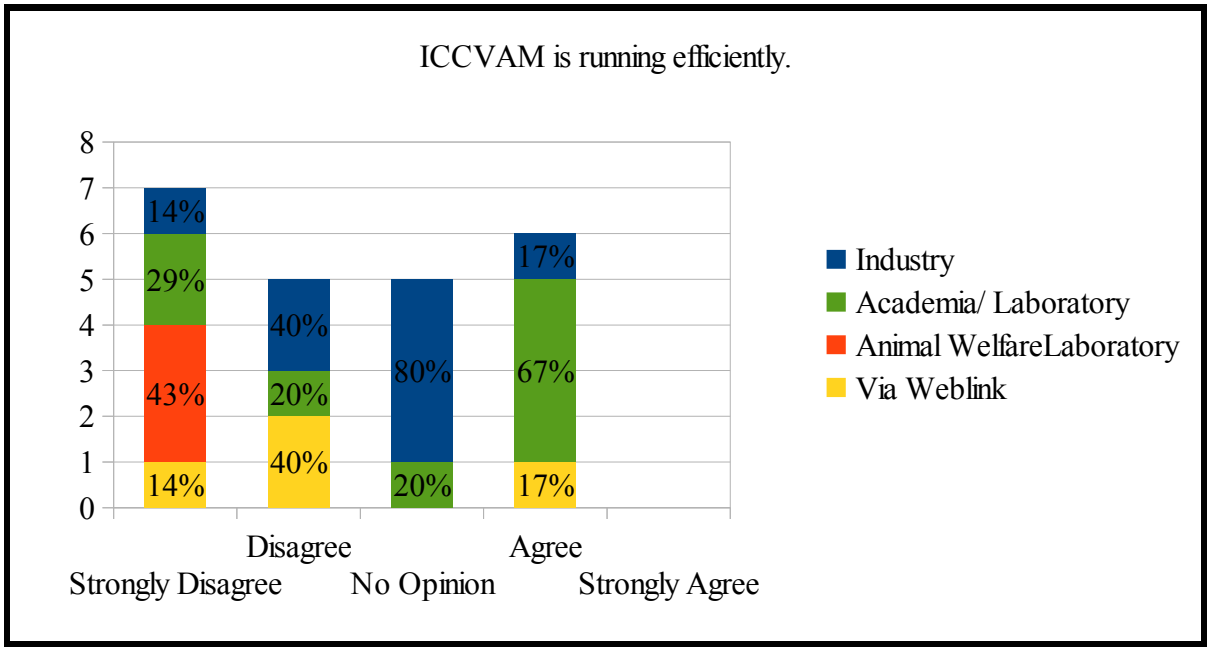
Figure 6 - Respondents' Answers to Statement #4



Regarding how efficient the ICCVAM is running, twelve respondents gave negative responses, versus only 6 who gave a positive response; and, not a single person strongly agreed with the statement. This statement was intended to gauge the perception of the respondents beyond whether they feel ICCVAM is meeting their own published mission statement sought to address how ICCVAM performs to the expectations that the respondents hold for ICCVAM. Twelve respondents did not think the ICCVAM model was running efficiently.

A mean score of 3.44 and 3.57 for statements 3 and 4 respectively, is strong evidence to support the hypothesis that there is a negative perception among relevant personnel regarding the performance of ICCVAM.

Figure 7 - Answers to Statement #4 by Demographic

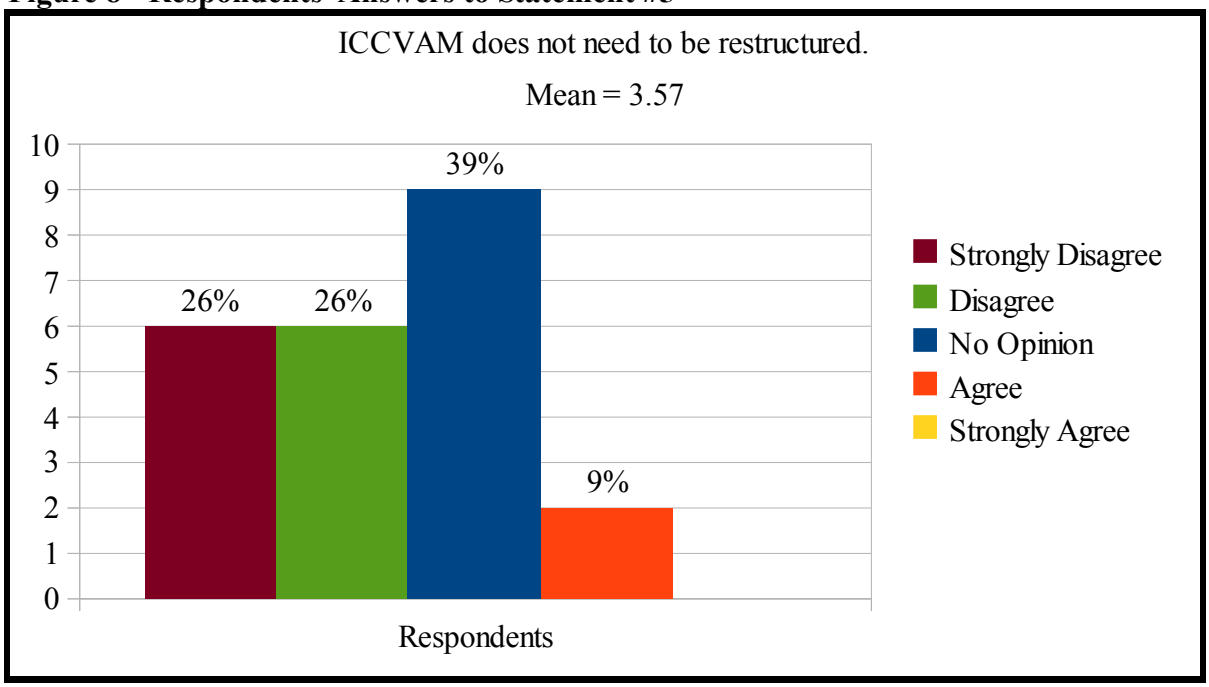


When the answers given for this statement are further analyzed, we see that the negative perception of ICCVAM's performance is not limited to one demographic, but all four categories.

<u>Statement #5</u>: ICCVAM does not need to be restructured.

This question was not asking for people to critique the performance of the ICCVAM, but gauged their opinion of how the ICCVAM is presently structured to carry out its mission. As it stands, ICCVAM consists of representatives from 15 different federal agencies who collaborate on efforts to review and advise the acceptance of alternative test methods. This is how it was established and now is a good time to reassess this model. With this statement we can see what people think about this.

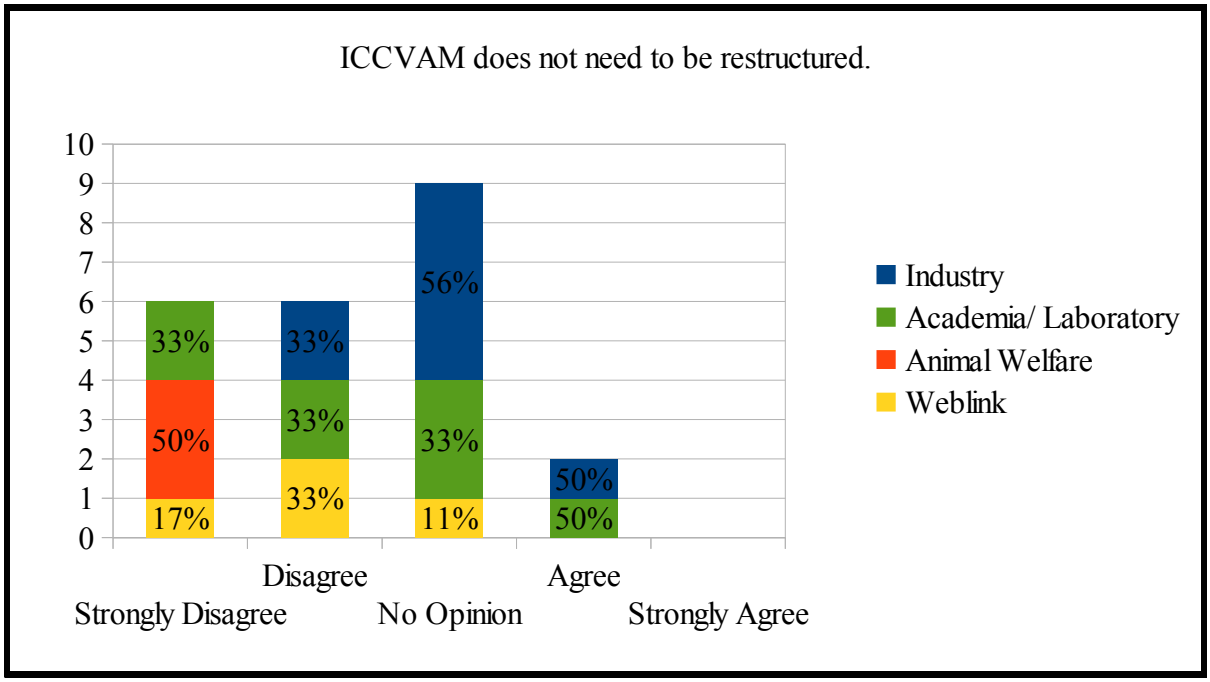
Figure 8 - Respondents' Answers to Statement #5



The number of respondents who replied to this statement was 23 with a mean answer score of 3.57. This score indicates that the majority of respondents, once again, answered in the negative, meaning most did not agree with the statement. While reading the answers to this statement it should be noted that they do not necessarily reflect the perception of the performance of ICCVAM, it does indicate however, that the majority of respondents were unhappy with the current format of the ICCVAM model.

Looking at Figure 9, each demographic group's answer in response to this statement is shown. Five of the eight respondents representing “industry” had no opinion on whether the ICCVAM model needed to be restructured at this point, which could mean that many people in industry are not familiar with how ICCVAM is structured to begin with. To obtain a better understanding, this could possibly be a more specific question that is addressed in future research.

Figure 9 - Answers to Statement #5 by Demographic



<u>Statement #6</u>: The US Government should increase the power currently bestowed upon ICCVAM to accomplish its mission.

Statement #6 differs from the previous Likert-scale statements (3,4, and 5) in that it is not asking for the respondent's opinion on the job being performed by ICCVAM, but whether or not they think the committee would benefit from an increase in power from the Federal government. The limitations of a questionnaire of this type keeps these answers from revealing exactly what kind of power the respondents, who agree with the statement, would like to see ICCVAM given, but it served to answer whether they felt this was a good idea. Some personal interviews did reveal opinions about what kind and how much power should be further given to ICCVAM for its mission.

Figure 10 - Respondents' Answers to Statement #6

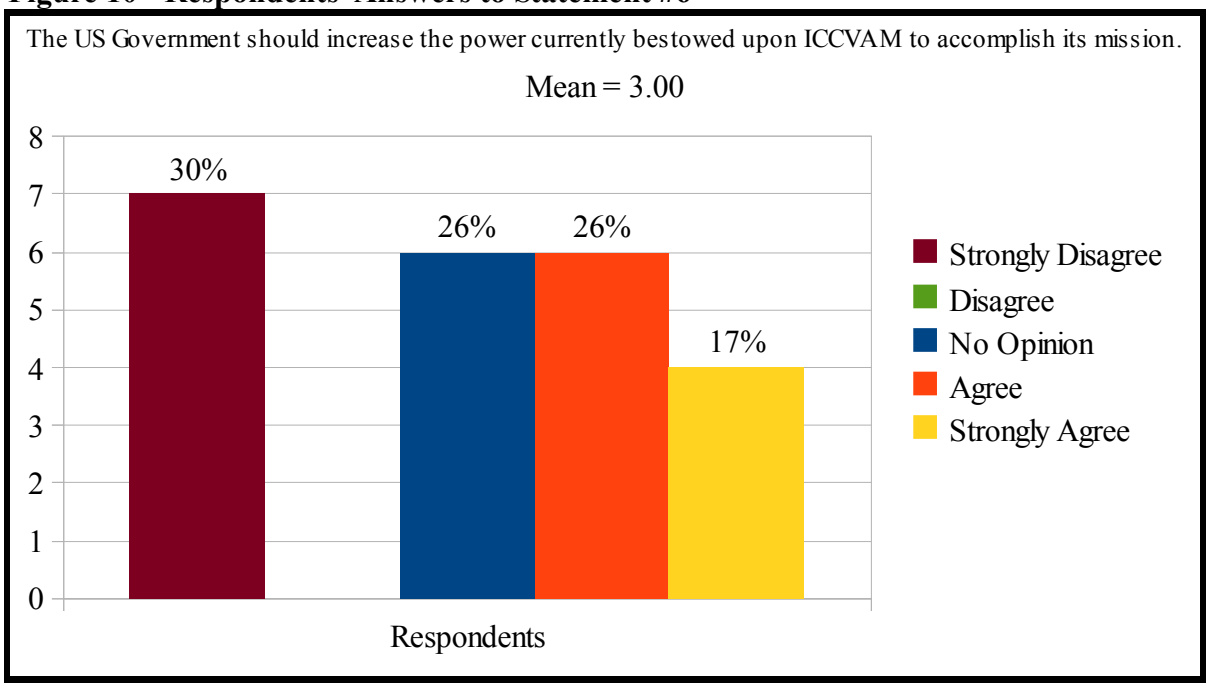
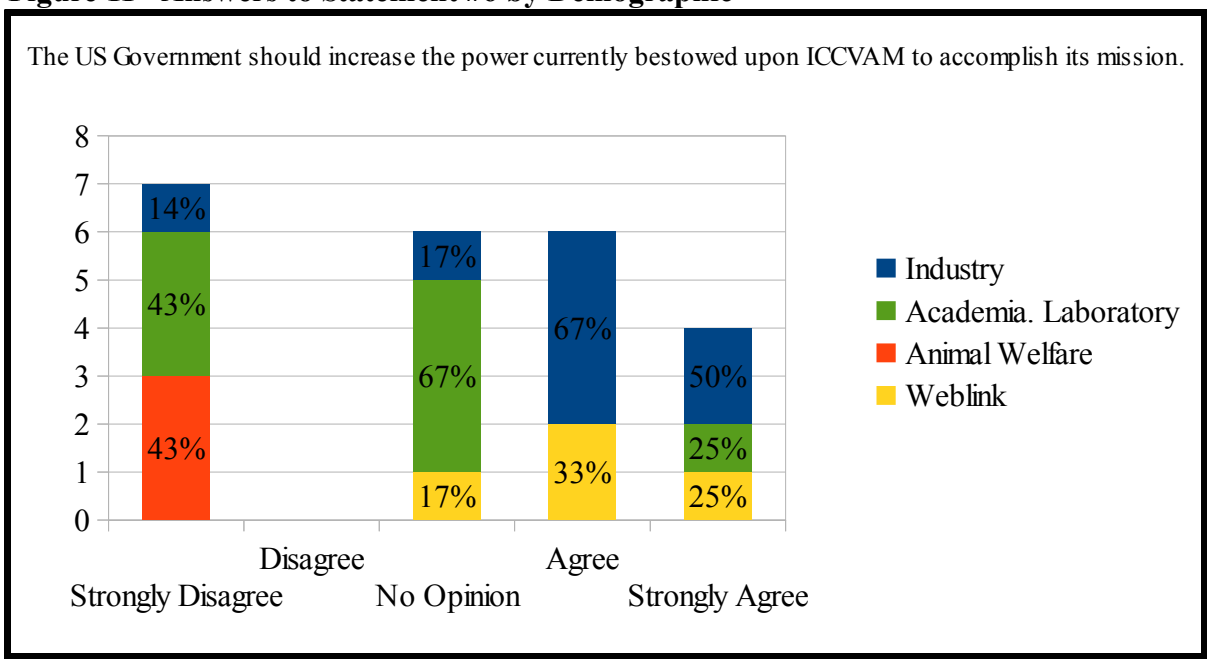


Figure 11 - Answers to Statement #6 by Demographic



For those that disagreed with this statement, it was emphatic. No respondent answered with "Disagree" for this statement and there were actually more respondents who agreed with the statement. This question was designed to gauge the opinion on a suggestion of what could make

the ICCVAM process more efficient. It could also be argued that this indicates how many people have enough confidence in the current ICCVAM model to think it would benefit from more power.

<u>Statement #7</u>: There are no other ways to accomplish the mission of ICCVAM.

This statement gauged the respondents' perceived value of ICCVAM as a way of getting alternative test methods accepted. When constructing this statement, the intention was to get an idea of whether people think the ICCVAM model is vital in accomplishing the stated mission of facilitating the development, validation, and regulatory acceptance of alternative test methods.

Figure 12 - Respondents' Answers to Statement #7

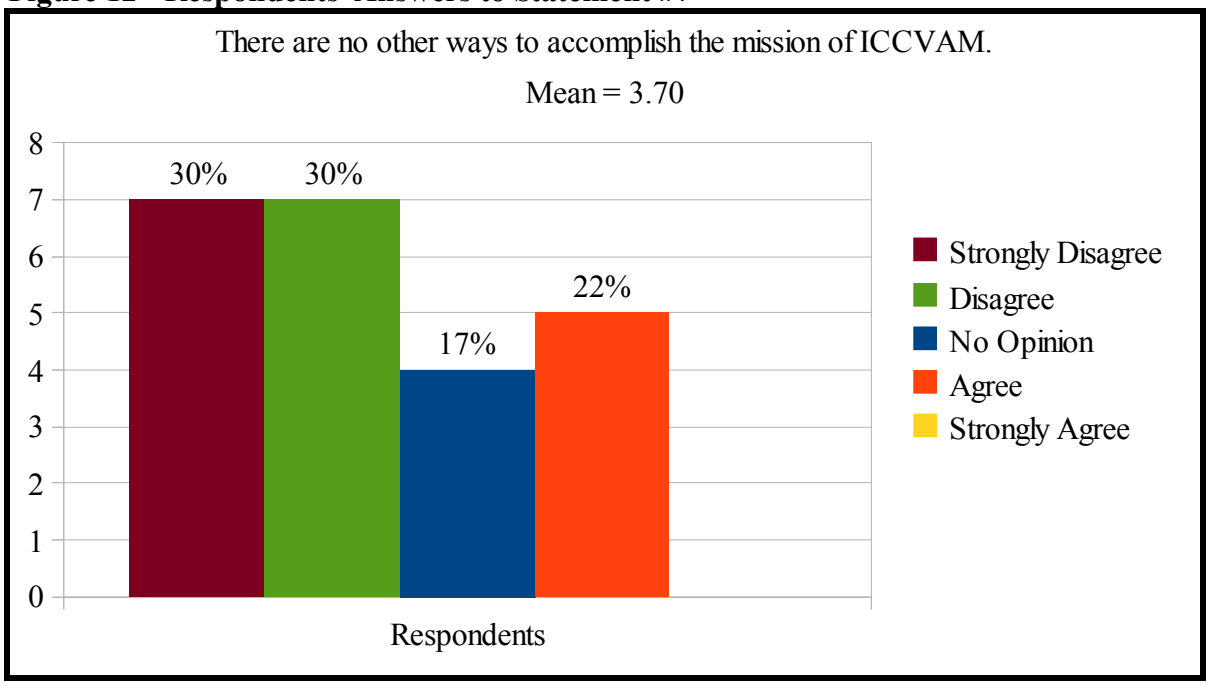
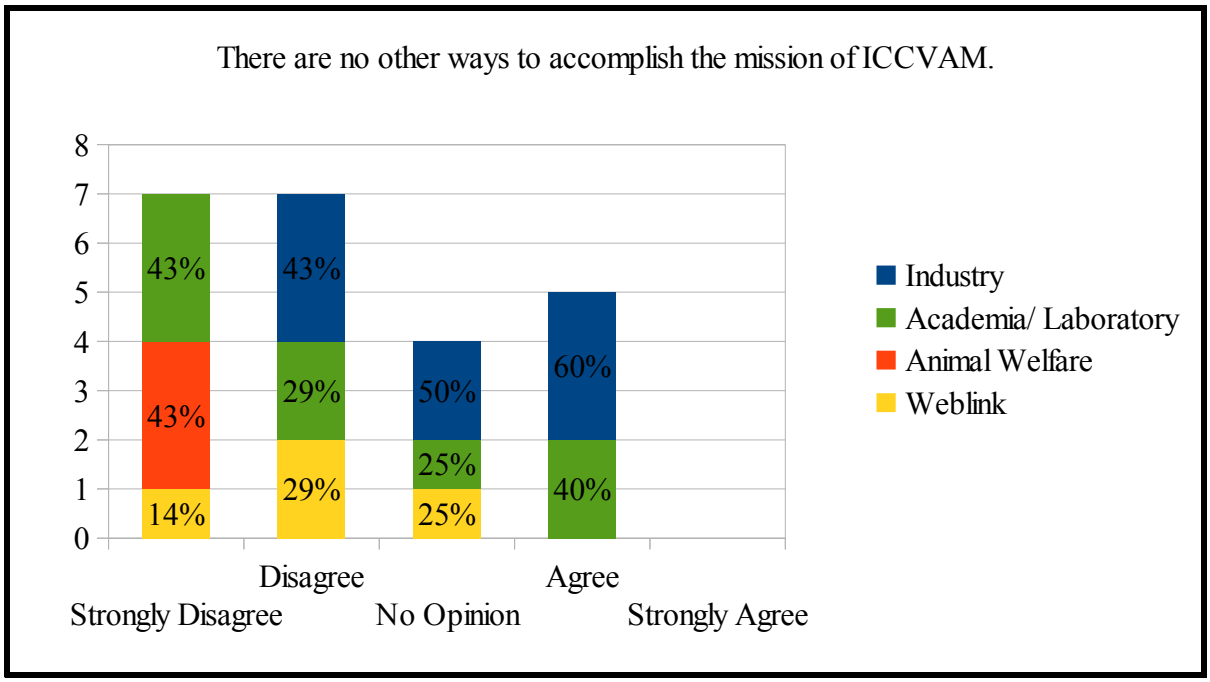


Figure 13 - Answers to Statement #7 by Demographic



Interestingly, the mean value of the answers about from this statement's answers is the highest of all from the questionnaire. Sixty-one percent of the respondents said they either strongly disagreed or disagreed with this statement compared to only 22% who stated that they agreed. However, coupled with information collected during personal interviews, the sentiment present among some of the respondents was that while ICCVAM is not necessary in getting alternative test methods accepted by regulatory agencies, it is still beneficial to have such a resource in place regardless of whether is meeting certain expectations or not.

Personal Interview Data

Personal interviews were conducted. At least one person from each of the three identifiable demographic categories was interviewed to reveal the particular sources of some of the perceptions held in regards to ICCVAM's performance.

Important information such as why the respondents felt the way they did, could not be accurately captured by the use of questionnaires. This is why the use of personal interviews was necessary. These personal interviews were aimed to help understand why this negative sentiment was present.

To yield valuable representative data, the aim was to speak with a cross section of people who are involved, in some way or another, with the mission of promoting alternative testing methods that adhere to the Three R's. All of the interviewees were found to have extensive experience with dealing with ICCVAM. When talking with these people, there was no indication of any grievance toward anyone actively working as a member of ICCVAM, but rather a frustration with the process as a whole.

The oral responses given to the interview questions were evaluated for overall attitude toward the performance of ICCVAM. The results of these interviews showed that every interviewee, with the exception of Dr. Stokes, had a negative perception of the performance of ICCVAM.

The lengthy interviews conducted with the sample population of personnel involved and/or intimately familiar with the ICCVAM process, also revealed different perspectives, different expectations, and even different ideas for the future of ICCVAM. However, there were some points that were consistently brought up by the interviewees as being sources of their disappointment. Below are the topics most consistently brought up by the interviewees during the interview:

1. Lack of Proactive Approach
2. Over-Rigorous Review Process
3. Limited Power

Chapter 6

CONCLUSIONS AND FUTURE WORK

Discussion of Data

With a range of mean scores from 3.00 to 3.70 for the questionnaire statements the hypothesis has been accepted. The data from the questionnaires indicate that ICCVAM is not meeting their expectations, and the information gathered from the personal interviews provides further data to support this. All of the interviewees, except Dr. Stokes, expressed a feeling of disappointment with the current state of the ICCVAM. Some said they were very optimistic in 2000[55], when ICCVAM became a permanent government committee, but have become somewhat disheartened over these 11 years. Whatever expectations were held by the interviewees, they have not been met. Jessica Sandler, of PETA, stated, "we worked very hard for the legislation that put ICCVAM into place...and we did have high hopes."[55] Through the personal interviews, three specific aspects of the ICCVAM process were identified as needing improvement.

The lack of a proactive stance by ICCVAM was one area discussed by all of the interviewees with the exception of Dr. Stokes. The process by which ICCVAM reviews test methods requires a sponsor being proactive enough to bring forth a nomination or submission for review. According to Catherine Willett, Science Policy Advisor at PETA, ICCVAM "does not go out and actively solicit methods from companies". She feels ICCVAM needs “to take an active role in identifying promising methods by going to meetings, by talking to manufacturers, by reading avidly about technology that's going on." She went on to say that, "ICCVAM needs to address agencies' needs. The agency has information needs and you have to make sure that when

you are validating a method that those needs are being addressed and you have to do that by communicating with the agency."[12]

This thinking was echoed by other interviewees; "It (ICCVAM) was very slow to adopt a proactive posture rather than to be simply reactive to what comes through the door", responded another[56].

Dr. William Stokes, Director of ICCVAM, addressed this in his interview by saying, "ICCVAM is a committee and so ICCVAM reviews methods that have been validated by other organizations that have the scientific resources to do that." It is true that NICEATM carries out validation studies, but he points out that, "validation is a very expensive activity. What we need is for other organizations out there that have resources, whether its academic institutions or non-profit organizations, to actually carry out validation studies to demonstrate that these new methods can provide that same level of protection and we need them to develop those methods."[57]

When the question of how the ICCVAM process could run more efficiently was asked, all the respondents mentioned how they felt the review process in general was too critical of the nominated or submitted alternative method and was too time-consuming.

"The ICCVAM process got bogged down in this over-rigorous thinking that went into what validation means", said Dr. Chad Sandusky, of The Physicians Committee for Responsible Medicine. "How do you validate a non-animal method against animal data when one of your central working theories is animal data are poor predictors?"[58]

Other respondents spoke of the fact that during the review process, the reference methods are regarded as being satisfactory and the potential alternative test method is "pick(ed) apart"[56].

Essentially, the alternative tests are held to an unfair standard, which the reference test is not[57]. As one respondent pointed out however, "Is all of that ICCVAM's fault? No."[56]

In another instance of consideration for ICCVAM, a different respondent replied, "Even ICCVAM is having problems. The whole...validation process is very time-consuming and cumbersome and it might not be necessary to be so hyper-sensitive."[59]

A paper written by Martin Stephens of the Humane Society of America offers recommendations for the ICCVAM process by addressing certain questions when using a reference method such as, "Does the reference method yield reproducible data within and between laboratories? In other words, how well does it predict itself? And what is known about its other limitations, such as subjective scoring, irrelevant dosing, over- or under-prediction, etc.?" He goes on to state, "lack of attention to these issues has led ICCVAM review panels to uncritically accept the reference standard as the 'gold standard'."[60]

To be fair to ICCVAM, it is a very important balancing act that ICCVAM has to deal with. The committee has to always consider the safety of an alternative test method. Anything that is going to possibly have an effect on humans, such as those in clinical research, has to be reviewed under the strictest of standards. At the same time however, ICCVAM recognizes the benefits of potential alternative test methods and that the faster the implementation of them, the faster the benefits are reaped by everyone involved.

Dr. Stokes, himself, recognizes this arduous process as he said, "It (the ICCVAM review process) is a lengthy process and it is expensive and those are probably two of the reasons why there are not more that have been brought to us."[57]

This brings up an important aspect of the ICCVAM process - funding. ICCVAM requires money to carry out its activities and the more money it can get, the more resources it could

employ to expedite more test reviews. One respondent suggested that they solicit funding from outside sources since they did not originally fight for a sufficient budget[56]. Lobbying for contributions from outside sources would also bring about more awareness for ICCVAM and its plight. As was proven with the data collected from the questionnaires, visibility is an area that could use some improvement and activities that would involve educating people about the ICCVAM process, and how it could be of even more benefit with more funding, could bring about a lot of good.

A major step in enhancing the ICCVAM process was discussed earlier: the ICATM agreement. Dr. Stokes has stated this agreement "will speed the adoption of new test methods"[61] by allowing ICCVAM to "leverage resources"[57] from international groups.

Finally, as alluded to earlier, there are glaring limitations to exactly what ICCVAM is allowed to do as far as getting alternative test methods validated and accepted by federal agencies. In Section 5(b) of the ICCVAM Authorization Act of 2000, it states, "Nothing in this Act shall prevent a Federal agency from retaining final authority for incorporating the test methods recommended by the ICCVAM in the manner determined to be appropriate by such Federal agency or regulatory body."[14] Unlike their European counterpart, the ECVAM, ICCVAM can only recommend that an alternative test method be accepted by various federal agencies. What this essentially means is that if sponsoring entities choose to submit their testing method for the long and tedious ICCVAM review, there is not a guarantee that it will be sufficient for the respective approving agency. The best a sponsoring company can hope for after nominating or submitting a new test method is a recommendation from ICCVAM. It is still ultimately up to whichever agency oversees the sponsoring company's product to approve the assay. As Kate Willett put it, ""Europeans are committed at the legislative level to replace animal use for all

kinds of scientific endeavors."[12] Again, the European Union has actually imposed deadlines for a couple of traditional animal tests to be replaced. Unfortunately for many, the U.S. government is not quite as committed.

Furthermore, while NICEATM, the administering body of ICCVAM, can conduct validation studies, it has to pay for contract laboratories to do such, while its European counterpart, ECVAM owns several laboratories[27] which makes being proactive and doing its own validation work much easier.

An important point when reading this information is that the sentiments of the respondents are not necessarily directed at the individual performance of those involved with ICCVAM. Many of the criticisms presented here are actually directed at the constraints and restrictions with which the committee has to work within. As Dr. Stokes said, the committee has "got hard-working people... that take their jobs very seriously."[57] These hard-working people are charged by law to work towards the goal of reducing, refining, or replacing animal test methods and have accomplished a great deal in these past 11 years. Unfortunately, judging by the data collected for this thesis project, many involved in pre-clinical testing, for whatever reason, do not feel this progress has been enough.

We now know the perception that is out there, but what is the reality? According to it's own website, ICCVAM has now successfully reviewed and recommended 42 alternative test methods that adhere to the Three R's[56]. Twenty-three of these test method reviews have come within the last three years, which is when Dr. Stokes stated ICCVAM increased its staffing. This is far more than any other group in this country has accomplished towards this mission[57]. "It would be a mistake to say we are better off without it (ICCVAM)", conceded one respondent[57]. "I'd rather improve ICCVAM than just dump it", replied another[58]. If nothing else, the very

creation of ICCVAM is seen as one giant step in the right direction. This could all boil down to more of a public relations issue than anything else. We see what the addition of staff has done for ICCVAM as far as test methods review, maybe it's time to put forth some effort into promoting ICCVAM and its potential benefit to anyone wanting more evolved test methods.

A related issue is one of general visibility. As previously shown (Figure 3), only 55% of the 42 respondents to the questionnaire, who stated that they had an interest and/or involvement with pre-clinical research, were even familiar with the work ICCVAM does. ICCVAM has been a permanent federal committee now for over 10 years and the fact that such a high percentage of respondents are unaware of what they do indicates a possible problem with the promotion of ICCVAM as a resource. The bottom line is that ICCVAM does have a higher success rate of getting alternative test methods presented to them accepted by appropriate agencies than any other group, but cannot be optimally effective if people are not aware of the work it does. Pre-clinical research personnel and anyone else who might be involved or interested in some way need to be aware of ICCVAM's availability as a resource.

Recommendations

The response data from statement #6 of the questionnaire indicates how many people think the ICCVAM model would benefit from increased power from the government. As discussed earlier, other groups like ECVAM are given greater power and resources in getting alternative test methods validated and accepted. A larger staff with their own laboratories are invaluable resources enjoyed by ECVAM but not ICCVAM[24]. This could possibly be a future reality for ICCVAM if given more funding.

To lobby for more funding, ICCVAM needs to present more definable achievements. To accomplish this, deadlines for goals need to be set, published, and met. It would be beneficial to collaborate with current critics of the ICCVAM process to establish these goals and deadlines so everyone will have a realistic idea of how long it will take and what resources can be used to accomplish these goals. ICCVAM published a Five-Year Plan in 2008 that outlined certain goals for the future, but without deadlines, we are left with just a wish list.

Future Work

With the signing of the ICATM Agreement, increased staffing and new Deputy Director, Warren Casey, Ph.D. at NICEATM, all occurring in the past three years, it would be appropriate to revisit this research in another five years in order to give these resources time to have an impact on the overall performance of the ICCVAM process. Future research should include the previously used methodology so an accurate comparison of new data with the data presented here can be performed. The information taken from the personal interviews further identified areas that can be individually studied in future research. For instance, when constructing a questionnaire to collect information regarding public perception of ICCVAM in the future, it could focus on the areas that have been identified here as being been areas of discontent, such as the perceived over-rigorous review process.

Since this topic involves politics, it may be hard to obtain opinions from individuals close to the process who might give the best information for fear of retaliation for their criticism. One idea that could help with this desire for more privacy by potential respondents, is to mail the questionnaires to the sample population with return postage affixed. Sending the questionnaires this way ensures there is not a way to trace the respective responses back to an individual

subject. To track which demographic group the respondent is a part of, each questionnaire that is mailed out could be printed on a certain color paper correlating to a respective demographic group. When a respondent mails back a completed questionnaire, the researcher would be able to identify what demographic group the subject belongs in while not having an individual's identifying information. This extra measure of anonymity could be an incentive for more subjects to complete and return the questionnaire.

REFERENCES CITED

1. Lean G. FOCUS: Animal rights: The medical gains – even veterinary science has benefitted from testing. *Independent on Sunday*. January 21, 2011:19.

2. Hellenica. Aristotle's biology and medicine, discoveries, and opinions. Available at: http://www.mlahanas.de/Greeks/AristotleBiol.htm. Accessed on January 26, 2011

3. Russell W, Burch R. *The Principals of Humane Experimental Technique*. 1st Edition. London: Methuen & Co. Ltd; 1959: 238.

4. Balls M. Replacement of animal procedures: Alternatives in research, education and testing. *Lab Animals*. 1994 July 28. (2):193-211.

5. Smyth D. *Alternatives to Animal Experiments*. London: Scolar Press; 1978: 218.

6. Utilization and Care of Vertebrate Animals Used in Testing, Research and Training. *Fed Register* 1985;50:20864.

7. National Research Council. *Toxicity Testing in the 21st Century: A Vision and a Strategy.* Washington, DC: The National Academies Press; 2007. 1:4 p.

8. Petition to the US Food and Drug Administration for mandatory use of non-animal methods in the development and approval of drugs and devices [petition]. The Mandatory Alternatives Petition Coalition; 2007. Available at: http://www.neavs.org/betterscience downloads/Mandatory-Alternatives-Petition.pdf. Accessed July 15, 2011.

9. Dove, Alan. The search for animal alternatives *Drug Discovery & Development*. 2010; 13:(4):10-13.

10. The American Physiological Society. What Do USDA "Animal Use" Numbers Mean? American Physiological Society Policy Action Center. 2006. Available at:

http://www.the-aps.org/pa/resources/bionews/animalNumbers.htm. Accessed January 26, 2011.

11. Animal Welfare Act Amendments of 1970, Pub. L. No. 91-579. Sec. 3 Sub Sec. g. December 24, 1970.

12. Willett, K. Telephone interview. May 19, 2011.

13. The Johns Hopkins Center for Alternatives to Animal Testing. CAAT History. Johns Hopkins Bloomberg School of Public Health Web site. 2011. Available at: http://caat.jhsph.edu/about/history.html. Accessed January 26, 2011.

14. ICCVAM Authorization Act of 2000, Pub. L. No. 106-545, 114 Stat. 2722. Dec. 19, 2000.

15. NIH Revitalization Act of 1993, Pub. L. No. 103-43, Sec. 404C. Sub Sec. June 10, 1993.

16. National Institute of Environmental Health Sciences. *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods*. NIH Publication No. 97-3981, NIEHS, Research Triangle Park, NC; 1997.

17. National Toxicology Program. About the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). Available at: http://iccvam.niehs.nih.gov/about/about_NICEATM.htm. Accessed on February 12, 2011.

18. National Toxicology Program. Scientific Advisory Committee on Alternative Toxicological Methods. Available at: http://ntp.niehs.nih.gov/index.cfm?objectid=7201756D-BDB7-CEBA-FD6377A9354BA3F6. Accessed on February 12, 2011.

19.Franz N. Industry applauds testing law. *Chem Week.* December 2000; 12: 46

20. National Toxicology Program. ICCVAM Test Method Evaluation Process**.** Available at: http://iccvam.niehs.nih.gov/about/process.htm. Accessed on February 17, 2011.

21. National Toxicology Program. Nominations and Submissions**.** Available at: http://iccvam.niehs.nih.gov/SuppDocs/submission.htm. Accessed on February 17, 2011.

22. Schechtman L. Implementation of the 3Rs (refinement, reduction, and replacement): Validation and regulatory acceptance considerations for alternative toxicological test methods. *Institute for Laboratory Animal Research Journal.* 2002; 43 (suppl):S85-S94.

23. ICCVAM. *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods.* NIH Publication No: 03-4508. Research Triangle Park, NC:ICCVAM; 2003.

24. ICCVAM. *ICCVAM Test Method Evaluation Report: Current Validation Status of a Proposed In Vitro Testing Strategy for U.S. Environmental Protection Agency Ocular Hazard Classification and Labeling of Antimicrobial Cleaning Products*. Research Triangle Park, NC: National Toxicology Program; 2010.

25. National Toxicology Program. Session on ICATM at 50th Annual Meeting of the Society of Toxicology. Available at: http://iccvam.niehs.nih.gov/about/icatm.htm. Accessed on February 12, 2011.

26. Countries unite to reduce animal use in product toxicity testing worldwide [press release]. National Institute of Environmental Health Sciences; April 27, 2009.

27. European Centre for the Validation of Alternative Methods. About ECVAM. Available at: http://ecvam.jrc.it/. Accessed on March 7, 2011.

28. Munn, Sharon. (2011, December). Development and Validation of Alternative Methods [Power Point Slides]. 10th Anniversary REMA.

29. EU Directive 2003/15/EC

30. Regulation EC 1907/2006

31. EU Directive 86/609/EEC

32. JaCVAM. (2009, June). JaCVAM Update [Power Point Slides]. SACATM Meeting.

33. Han, Soon. (2011, March). The Korean Center for the Validation of Alternative Methods (KoCVAM): Recent Progress and Future Plans [Power Point Slides]. Society of Toxicology 50th Annual Meeting.

34. Health Canada. About health Canada. Available at: http://www.hc-sc.gc.ca/ahc-asc/index-eng.php. Accessed April 22, 2011.

35. Begley, S. Physician-researchers needed to move cures out of the rat's cage. *Wall St J*. April 2003: 1

36. Harding, A. More compounds failing phase I. FDA chief warns that high drug attrition rate is pushing up the cost of drug development. *The Scientist*, August 2004.

37. Lumley C, and Walker S. *In: Animal Toxicity Studies: Their Relevance for Man.* Quay, Lancaster, UK; 1990:73

38. Spriet-Pourra C, Auriche M. *Drug Withdrawal from Sale*. 2nd ed. New York, USA: Scrip Reports, PJB Publications; 1994

39. New England Anti-Vivisection Society. Benefits of Using Non-Animal Tests. Available at: http://www.neavs.org/betterscience/bettersci_benefits_of_using_nonanimal_tests_110101.htm. Accessed on March 13, 2011.

40. National Institutes of Health. *ICCVAM 2008-2009 Biennial Report.* Research Triangle Park, NC: National Toxicology Program; 2010

41. Weise, E. Three U.S. agencies aim to end animal testing. *USA Today.* February 14, 2008

42. British Union for the Abolition of Vivisection. Poll by Opinion Research Business 2004

43. Cengage Learning. Public opinion. Available at: http://www.cengagesites.com/academic/assets/sites/4620/samplechapter.pdf. Accessed on July 15, 2011.

44. Board of Health Sciences Policy. Challenges in Engaging the Public Policy Community. *Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary*. Washington, DC: National Academies Press; 2011:42.

45. Center for American Progress. Better, Not Smaller: What Americans Want From Their Federal Government. Available at: http://www.americanprogress.org/issues/2010/07/pdf/what_americans_want.pdf. Accessed on July 15, 2011.

46. Dumas J. Usability testing methods: subjective measures, part II - measuring attitudes and opinions. *Common Ground, the newsletter of UPA*.1998: 4-8

47. Sauro J. Survey items should include a neutral response: agree, disagree, undecided? Available at: http://www.measuringusability.com/blog/neutral-option.php. Accessed April 12, 2011.

48. Cooper C. Polling methods. *The Leader-Post*. November 29, 2001:B12

49. Dyer C. *Beginning Research in Psychology: a Practical Guide to Research Methods and Statistics*. Oxford, UK; Cambridge, Mass., USA: Blackwell; 1995.

50. Survey Monkey. Does adding one more question impact survey completion rate? Available at: http://blog.surveymonkey.com/2010/12/survey_questions_and_completion_rates/. Accessed on April 2, 2011

51. Creswell JW, & Tashakkori A. Developing publishable mixed methods manuscripts. *J Mix Methods Res*. April 2007; 1(2): 107-111.

52. Glaser BG. Getting out of the Data: *Getting Out of the Data: Grounded Theory*. Mill Valley, CA: Sociology Press; 2011.

53. Goetz JP, LeCompte MD. Ethnographic research and the problem of data reduction. *Anthropol Educ Q*. Spring 1981; 12: 51-70.

54. Thomas DR. A general inductive approach for qualitative data analysis. Frankumstein. 2003. Available at: http://www.frankumstein.com/PDF/Psychology/Inductive%20Content%20Analysis.pdf. Accessed July 20, 2011.

55. Sandler, J. Telephone interview. May 18, 2011.

56. Anonymous Respondent #1. Telephone interview. June 3, 2011.

57. Stokes, W. Telephone interview. June 9, 2011.

58. Sandusky, C. Telephone interview. June 3, 2011.

59. Anonymous Respondent #2. Telephone interview. June 8, 2011.

60. Stephens, M. Some Considerations as ICCVAM Moves Forward. Available at: http://alttox.org/ttrc/us/way-forward/stephens/. Accessed July 20, 2011.

61. ICCVAM. About ICATM. Available at: http://iccvam.niehs.nih.gov/about/icatm.htm. Accessed on April 27, 2011.