Comparing Animal Models and their Alternatives: Examining Ethical, Regulatory, and Technical Perspectives

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Part I: Introduction

Background

In 2021, COVID-19 was listed as the underlying cause of death for 415,399 deaths in the United States (Ahmad, 2022). In that same year, approximately 110,000,000 animals were killed for the purpose of research and drug development (Animal Testing Facts and Statistics, 2004). Because of their analogous physiological systems, biological similarities, and accessibility, animals have often been considered the gold standard for test subjects. Animals are considered a highly efficient means of testing drugs for any adverse effects due to their compact size, accelerated life cycles, and short gestation periods (Bryda, 2013). Scientists use animals to mitigate health risks to humans and to demonstrate the efficacy and safety of drug therapies. While animal testing has been invaluable in the past, new technologies such as biomaterials, synthetic tissues, and computation models are enabling more accurate representations of human tissue. In turn, this reduces the reliance on animal testing and gives new possibilities for drug testing and research.

To explore the influence of alternative models on the use of animal models, I first examine the role that animals have played in medicine throughout history. Additionally, I discuss the increasing prevalence and application of alternative models in more recent years. Alternative models or technologies are methods or techniques that can replace or mitigate animal models in research and testing. It is important to investigate the history of animal utilization in medicine in order to understand how it impacts the current landscape of animal use in research and therapeutic drug development. Scientists have made significant advancements in fields such as tissue engineering, leading to the emergence of alternative models that could potentially replace

animal models. In this paper, I investigate the ethics, utility, and regulatory aspects of both animal models and alternative models. This in-depth analysis enable us to gain a better understanding of the intricate interplay between these different approaches to research and drug development.

In this paper, I use actor-network theory (ANT) to analyze the relations and interplay between animal models and alternative technologies. ANT relies upon building a network composed of nodes that can either be human or nonhuman actors (Latour, 1992). Human actors can be individuals or social groups. Nonhuman actors represent everything else, including artifacts, technologies, or concepts. At its core, ANT assumes that all entities, both human and nonhuman, are equal in their ability to influence and shape the network. It focuses on how these actors interact and influence one another. While there is a clear distinction between human and nonhuman actors, the emphasis lies in that actors, regardless of their type, impart some influence on their system. By treating all actors as equals, one can focus on the relations and effects between various actors within a network. This approach facilitates the comparison and contrast of different aspects of the networks, providing a deeper understanding of the intricate interplay between actors in both animal models and alternative models.

Methods

This approach aims to understand the interactions between various actors within the context of animal models and alternative models using multiple methods. To achieve this, I first draw from historical data to lay the groundwork for the subsequent critical analysis. I then use literary analysis to examine how animal models and alternative models are used in therapeutic drug development and scientific research, both historically and currently. I use peer-reviewed

studies and scientific journals that focus on the use of animal models and alternative models, as well as related technologies, in our analysis. In turn, this provides insights into the technical utility and significance of both types of models, as well as offer a discussion of their accuracy and efficacy.

Secondly, I use policy analysis to assess the impact of alternative models on regulations by examining regulatory agencies, such as the United States Department of Agriculture (USDA), the Food and Drug Administration (FDA), and other committees. The analysis focuses on how regulatory agencies have influenced the adoption of alternative models in research and their regulation of animal models. I examine policies and guidelines issued by regulatory agencies and compare that to the trends in the use of new forms of alternative models. This analysis provides a comprehensive overview of the current regulatory landscape and offers insights into potential paths for future policies.

Finally, ethical frameworks including utilitarianism, deontology, and virtue ethics are used to gain a more humanistic perspective and asses the inherent ethical considerations with animal models and their alternatives. These frameworks enable us to explore different aspects of ethical decision-making, such as the consequences of using animals for research, the principles and duties that govern the treatment of animals, and the virtues that researchers should embody. Using multiple ethical perspectives enables us to gain a more comprehensive understanding of the ethical dimensions of animal research and alternative models. This, in turn, helps us better understand the networks that sustain animal and alternative models in research, including the actors involved, their roles, and their interactions in shaping the ongoing debate regarding the use of animals in research.

Part II: Animal Models

Background on animal models

Animal experimentation dates back to the 4th century BCE (Hajar, 2011). During these periods, animals were dissected by early Greek physician-scientists to understand their anatomy, physiology, and biological mechanisms (History of Animal Testing, 2023). Nowadays, animal models are used for a wide variety of scientific research and therapeutic drug development purposes. Animals allow us to identify potential side effects, determine optimal dosing, and study various diseases including cancer, heart disease, diabetes, and dementia (National Research Council, 1988).

While certain animals are chosen due to their genetic similarities to humans, the methods for experimentation have improved vastly over the past centuries. Certain animals share high degrees of genetic similarity, which make them a valuable subject for scientific research (Suntsova & Buzdin, 2020). The most commonly used animals since the 1980s have been rodents due to their size, cost-effectiveness, and ease of maintenance (Bryda, 2013). Humans and mice have physiological similarities which allow us to study disease and physiological processes in a controlled manner to help advance our understanding of human biology (Perlman, 2016). By observing the effects of drugs on animals, researchers can gain important insights into their interactions with organ systems, as well as their potential benefits and risks.

Technological Utility

While animal models may seem to be a comprehensive method for scientific and drug development, it's essential to recognize that they represent only one aspect of the process. The

research process typically begins with thorough investigations, preliminary calculations, and modeling. This, in turn, leads to studies that use tissue samples and non-invasive procedures before finally using traditional animal models (Mohs & Greig, 2017). Amid this process, animal testing serves a crucial role, but it is important to recognize that it is only a piece of the larger puzzle. Although animals do not perfectly represent human biology, their contribution to modern medicine cannot be overstated. Animal models have enabled numerous advancements that have saved countless lives. For instance, research on cows in the late 18th century led to the first vaccine, which targeted the smallpox virus (Riedel, 2005). The development of the oral polio vaccine was based on experiments conducted on primates (Bertrand, 2021). Additionally, in the 1920s, insulin was discovered through experimentation on canines, and diabetes research was founded on data gathered from genetically modified rodents (A. J. King, 2012). These examples demonstrate the vital role animals have played in scientific advancements and breakthroughs.

Animals played a critical role in the development of vaccines and medical treatments in the past when medical science was less advanced. However, as science progressed and became increasingly sophisticated, precision became more important to ensure that treatments are accurate to human physiological conditions. This shift toward more precise medicine has introduced skepticism about animal testing. In recent years, questions regarding the accuracy and efficacy of results from animal testing have been brought up (Akhtar, 2015). Other sources indicate that animal models may be poor indicators of drug safety within humans (Van Norman, 2020). Concerns about the reliability of animal testing results suggest that more subjects would be needed to demonstrate effectiveness (Macleod & Mohan, 2019). Other arguments revolve around inherent problems related to the interpretation of data and the application of results concerning animal testing (Balls et al., 2019).

Animal models have been essential in the past, but trends in the medical and research fields have raised questions about their necessity. Although animal testing is typically less expensive than other potential alternatives, the cost gap is beginning to narrow for certain types of alternatives (Meigs et al., 2018). However, there are established systems in place that support the ongoing use of animal models. For example, Contract Research Organizations (CROs), offer clinical trial services to major pharmaceutical companies through the use of large-scale animal testing (Meigs et al., 2018). Since animals have been used in testing for centuries, transitioning to a new means of testing will be difficult regardless of the costs. Despite any challenges and criticisms surrounding animal testing, it remains a staple in the research and drug development processes and is likely to continue to be for the foreseeable future.

Regulatory

Regulatory frameworks often prioritize patient safety which often impedes rapid innovation, leading to gradual advancements and changes in the medical field (Field, 2008). Ensuring that drugs and therapies are produced according to regulatory parameters and are safe for patient use is paramount. A large part of this assurance comes from animal testing, which is regulated by various agencies such as the USDA (National Research Council, 2004).

The Laboratory Animal Welfare Act was the first federal law regulating animal research. This law mainly aimed to prevent pet resale to research facilities (Cardon et al., 2012). Throughout multiple amendments, the act continued to improve the standard of care for animal treatment within research. This law is now known as the Animal Welfare Act (AWA) and is the primary federal law that regulates the treatment of animals and is enforced by the USDA.

All institutions and organizations with animals under AWA are required to have an Institutional Animal Care and Use Committee (IACUC) which oversees and reviews all animal experiment protocols (National Research Council, 2004). While AWA sets the minimum standards of care and treatment for animals in research, it is important to note that rats and mice, which make up 99% of animals used in research, are excluded (Carbone, 2021). This means under federal regulations, experimentation that causes physical or psychological harm to mice and rats is legal. Although there was a push towards the inclusion of animals like mice and rats in AWA, the National Association for Biomedical Engineering strongly opposed the notion and prevented the amendment due to the alleged costs associated with such changes (Rats, Mice, and Birds, n.d.).

Other agencies such as the Public Health Service (PHS) have policies for the standards of animal care that cover all vertebrate animals (Public Health Service Policy, 2015). However, adherence is not required unless the research is funded by the PHS. Additionally, Good Laboratory Practices (GLP) are required for any nonclinical laboratory studies which include organizations and companies relating to pharmaceutical development that could avoid PHS policies (Good Laboratory Practice Regulations, 1979). These strict regulations provide a framework to provide proper housing, feeding, handling, and care of animals (Good Laboratory Practice, 1978). However, the GLP regulations do not explicitly address the humane treatment of animals used in nonclinical laboratory studies. Overall, there are a wide variety of regulatory agencies and regulatory guidelines imposed on the treatment and use of animals. Acts such as AWA provide a foundation for treating animals, but there are still issues concerning the scope of these regulations.

Ethical

The controversy surrounding animal experimentation stems from the harm animals endure for the benefit of humans. Is there an acceptable amount of pain, suffering, and death of animals that justifies the human benefits? While humans can know and understand the consequences of an action, such as a strenuous physical activity that leads to muscle soreness, animals are never given a choice. It can be conflicting to both feel empathy for the suffering and death of animals, while also acknowledging the importance that animal testing has had on society. This raises the question: what does it mean for something to be ethically or morally right? While there is no perfect definition of ethics, it can be described as standards of right and wrong that help dictate what humans ought to do in terms of their rights and obligations to society (Velasquez et al., 2010). Although a definition of ethics alone can not definitively dictate what is morally right or wrong, frameworks such as utilitarianism, deontological ethics, and virtue ethics can offer perspectives through which we can view a particular situation or issue.

A utilitarian perspective, which seeks to maximize happiness while minimizing suffering, may consider minimal amounts of harm to animals as justifiable when weighed against the significant benefits to humans (Utilitarianism, 2021). However, when greater amounts of harm and death occur, the justification becomes more difficult, especially if there are alternatives. Deontology is concerned with the inherent morality of an action, and thus, it is essential to consider its principles in relation to animal testing (Deontology and Animals, 2013). The harm caused to animals during testing may not be justifiable under deontological principles, regardless of potential benefits. However, this could vary depending on the specific context and ethical considerations. It is challenging to assess the ethical implication of animal testing from the perspective of virtue ethics, which prioritizes virtues over adherence to strict rules. (Walker,

2016). On one hand, the use of animal testing may be acceptable if it is conducted with a commitment to promoting the welfare of society. On the other hand, it could be argued that by sacrificing animals, respect for life is already being violated and therefore it is not ethically justifiable.

In the context of ethical frameworks, animal testing can be viewed in various ways, and there may not be a simple answer of right or wrong. The continued push towards more strict and humane regulations and the use of alternative models give some reason to believe that society has deemed animal testing unethical. However, a majority of people still agree that the ends justify the means for animal testing in science and research (Festing & Wilkinson, 2007). As we move forward, it is important to consider the potential future of animal testing and continue to critically examine the use of animals in research.

ANT Analysis

Actor-network theory (ANT) can offer valuable insights into the practice of animal testing and its broader implications for society. By examining the various human and non-human actors involved in animal testing, including scientists, regulators, and laboratory animals, we can gain a deeper understanding of the complex network that sustains this practice. The utility of animal testing is an important node within this network regarding the technical abilities and advancements resulting from animal models. Ethics are another crucial node, as they define the moral boundaries of animal testing and shape our perception of its acceptability. Finally, regulations represent a final key node that set the legal standards that govern animal testing and ensure that it is conducted safely and responsibly. Together, these pieces interact with each other

and with other actors within the network, such as the pharmaceutical industry and animal rights activists, to shape the ongoing debate regarding the use of animals in research.

Animal testing has played a vital role in advancing medical treatments, including vaccines, antibiotics, and disease therapies. The utility of animal testing is a key factor in this process, shaped by various social and material actors, such as funding sources, regulations, ethical considerations, researchers, procedures, equipment, and the animals themselves. These actors interact with each other, shaping the technical utility of animal testing and the overall network. As the network evolves over time, shifts in funding or equipment may also impact the utility of animal testing.

Regulatory agencies have a large role to play within the network of animal models. They dictate the legality and the regulations to be followed for the proper use of animal experimentation. A multitude of other actors shape regulatory agencies such as governments, ethics, funding, and cultural norms. The interconnectedness of these actors influences how regulatory agencies control animal testing. As cultural norms shift, so does the pressure on agencies to alter existing regulations.

Ethical considerations help define right and wrong in the eyes of society. This includes moral and philosophical perspectives on the use of animals in scientific research. Ethics committees, which are composed of researchers and other experts, often play a key role in shaping ethical standards for animal testing (M. King & Zohny, 2022). However, the broader network of actors also plays a role in shaping these ethics, including the public, cultural norms, animal rights activists, and regulatory agencies. While the ethical standards may not be as directly disruptive as regulatory agencies in the scope of animal testing, it provides powerful insight into the direction of scientific advancement.

All of these systems are dynamic in nature, they are constantly evolving and changing according to stimuli within the network. The ethics, regulations, and utility, with respect to animal testing, are connected by more than a single node. Each of them is distinct in its own right but also connected to each of the other nodes, which makes for highly complicated systems where changes can have truly rippling effects. Using ANT to examine animal testing, we can gain a more comprehensive understanding of various actors, what roles they play, and how they interact with each other to shape the use of animal models in society.

Part III: Alternative models

Background on alternative models

In 1959, William Russel introduced the goals of replacement, reduction, and refinement of animal testing (Hubrecht & Carter, 2019). This marked one of the earliest steps towards the responsible use of animals in research. These goals advocated for the refinement of animal use to minimize suffering and the use of alternative models wherever possible. The inception of cell culturing, a process that entails growing human cells outside the body, served as a foundational technique in the pursuit of achieving these goals. Researchers did not design cell culturing techniques to replace animal models, but they have become a cornerstone of modern research, paving the way for the development of new technologies and techniques.

By the late 1980s, a new field known as tissue engineering began to emerge (Rogers, 2018). Tissue engineering involves the application of engineering and biological principles to create tissues that can replace or help repair damaged tissue. Tissue engineering places a major emphasis on creating tissue constructs that can also perform the same complex biological

functions as native tissue (Rogers, 2018). In recent decades, other fields have also begun playing a role in alternative models and methods. Advancements in fields such as computer science have significantly increased computational power, enabling the execution of highly complex simulations (Sorguven et al., 2021).

Bioinformatics is an interdisciplinary field of biology and computer science that seeks to understand biology through the use of computational analysis (Bayat, 2002). Furthermore, researchers have utilized nanoscale materials and properties to develop innovative medical applications, which has led to the emergence of nanomedicine (Anjum et al., 2021). Advancements in science and technology have led to the development of new fields, that offer highly sophisticated tools and techniques for gaining a deeper understanding of complex biological processes and systems.

Technological Utility

The advent of new technologies has ushered in unprecedented possibilities for medical and scientific advancements that have created opportunities to reevaluate the role of animal models. Although fields like tissue engineering and nanomedicine were not intended to replace animal models, they offer a level of technical progress that may very well shift the current paradigm. Examples of these technological achievements include organoids and drug-carrying nanoparticles (Doke & Dhawale, 2015). These technologies enable researchers to create human-like tissue and investigate the mechanistic behavior of tissue and particle interactions. Exploring more complex biological mechanisms could minimize the need for animal testing and produce safer medications, and even reduce the need for such rigorous trials to prove their safety and efficacy.

In vitro models are experiments conducted outside of a living organism, which often includes growing cells within controlled environments. These types of experiments can allow researchers to control variables to investigate specific tissue or disease mechanisms. However, they can not fully replicate in vivo tissue. Stem cells, which are cells that can differentiate into specialized cell types, allow researchers to create environments composed of native-tissue-like cell compositions (Stem Cell Basics, 2016). By using stem cells, researchers can create more accurate models to study human biology and create and test new therapies. However, stem cell research is an ongoing process, and many of their mechanisms are still unknown (Stem Cell Basics, 2016).

Organoids, which are 3D structures derived from stem cells, present a unique opportunity to mimic more complicated structures found in specific tissues or organs. The first long-term organoid was created in 2009 and utilized a single stem cell to create a 3D cultured intestine organoid (Corrò et al., 2020). These organoids have been shown to recapitulate the architecture and function of human organs more accurately than monolayer cultures (Heydari et al., 2021). An example of another technology is organs-on-chips, which are small-scale devices that can artificially mimic the structure and function of native organs. These devices can include human cell microenvironments designed to mimic human tissue (Leung et al., 2022). Systems such as these also allow researchers to mimic the function of our heart, kidney, lungs, and other organs (About Tissue Chip, 2015). Other than in vitro technologies, computer simulations have become another method of conducting research that would have typically been done on animals. Computer models do not require physical resources, but instead, perform calculations based on sets of conditions and parameters to produce a result. For instance, one research team found that

their computation model was able to predict heart toxicity as accurately as traditional experimental methods (Passini et al., 2017).

Toxicological tests are one major area of interest for alternative, non-animal models and have seen success in preclinical screening because of their simplicity compared to other tests (Doke & Dhawale, 2015). StemoniX, a company specializing in alternative models for drug toxicity testing, has developed what they call microOrgan plates capable of evaluating neurotoxicity and cardiotoxicity in artificial systems (Powell, 2018). Other companies, such as Corning, have developed systems that utilize in vitro technologies for high-throughput drug screening (Powell, 2018). The emergence of companies whose focus is on replacing animal testing validates the technical ability of these emerging technologies. While alternative models may not have the same technical capabilities as animal models, the paradigm is beginning to shift as innovations continue to advance alternative technologies.

Regulatory

Although new alternative models and methods are constantly being developed that may replace animal testing for certain purposes, regulatory agencies have been slow to integrate these changes into current regulatory frameworks. Nonetheless, in recent years there has been a growing push to reduce animal testing, particularly because of continued advancements in alternative methods (MacArthur Clark, 2018). To improve animal welfare, the principles of replacement, reduction, and refinement, also known as the 3Rs of animal testing, are being increasingly recognized by regulatory agencies (Hubrecht & Carter, 2019).

While alternative methods may be used in some circumstances, such as in preliminary research and development, their widespread use and acceptance may be limited without the

adoption and integration by regulatory agencies (Doke & Dhawale, 2015). Consequently, animal testing would continue to be the standard practice for ensuring safety and efficacy. For alternative testing methods and models to be widely accepted, they must undergo rigorous testing and validation to ensure that they provide results that meet predetermined standards.

The introduction of agencies such as the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) has been established to help promote alternative models and their validation for use as replacements for, or in conjunction with, animal testing (National Toxicology Program, 2022). The ICCVAM is composed of representatives from various federal agencies and their primary function is to facilitate regulatory acceptance of test methods that can reduce the need for animal testing. Furthermore, they provide recommendations to other federal agencies in terms of regulatory decision-making that can impact the use of alternative methods. Another closely related agency is the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which provides scientific and administrative support for the ICCVAM (NICEATM: Alternative Methods, 2021). In the 2018-2019 Binmial Progress Report, the ICCVAM describes its ongoing work to develop alternative methods for regulatory testing, in areas including acute toxicity, skin sensitization, and eye irritation (Interagency Coordinating, 2020). They also launched a new initiative to develop and validate alternative methods that can be used in evaluating medical devices. Furthermore, they have been improving relations with international organizations such as the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM). Although these do not indicate an immediate replacement of animal models, they provide evidence that changes are underway.

Current regulatory frameworks are more advanced and established for animal models than for alternative methods. Without the approval of regulatory agencies, widespread adoption will not occur regardless of any technical achievements. Progress is being made by groups such as the ICCVAM, which show that regulatory change is possible and promotes the continued use and development of alternative models. Furthermore, the recognition of the 3Rs shows promise for the use of non-animal methods and models in the regulatory space.

Ethical

A key component of alternative models is the consideration of the effects, or lack thereof, on animal welfare. Even if alternative technologies do not require the use of animals, the question arises whether they should still be used if they are not at least as accurate and reliable as their animal experimentation counterparts. While it may seem intuitive to replace animals with equally reliable and accurate alternatives, the assessments of such metrics in the real world are often complex and may not have a straightforward answer (Bruton et al., 2000). In addition, implementing alternative methods and models may require significant investments in new machinery, training, and research to ensure their reliability and validity, and to obtain regulatory approval.

The use of alternative models can also be viewed through the lens of ethical frameworks. From a utilitarian perspective, the use of alternative models would likely be justifiable so long as they achieve an equal or greater level of efficacy, thereby maximizing the well-being of both humans and animals (Utilitarianism, 2021). Deontology would likely align with the utilization of alternative models because they do not cause harm and overall pose a benefit to society (Deontology and Animals, 2013). Virtue ethics would likely view the use of alternative models

as ethically justifiable, as utilization of these models promotes positive virtue with the goal to further scientific knowledge and enhance the overall societal welfare (Walker, 2016). These frameworks generally find alternative models to be ethically justified, however, that is under the assumption that the results are accurate and it does not result in additional and unnecessary harm to humans.

Using animal alternatives appears to be much less ethically controversial than using animal models. However, it is important to note that some models and technologies still require human cells, and as a such, the sourcing of cells can have ethical ramifications (Lo & Parham, 2009). There are other ethical considerations to take into account, such as ensuring the development and use of alternative models respect the rights and welfare of human participants. Even if alternative models appear to be more ethical than their traditional counterparts, it is vital to inspect the ethical implications of these alternatives in their own right.

ANT Analysis

Actor-network theory can offer valuable insights into the wider societal implication of using alternative models over animal models. Examining the various human and non-human actors involved can help us gain a deeper understanding of the complex network that sustains this practice. The technical utility, regulations, and ethics each play important roles within the network and are constantly influencing one another.

Alternative models such as organoids, microfluidics, and computational models have shown great potential for advancing medical treatments and scientific discoveries, including drug development and disease research. The utility of these models is a key factor in this process, shaped by various social and material actors. One of the major factors is technologies that have

allowed such advancements, as well as institutions like universities that provide knowledge to researchers. Furthermore, there are other actors such as the researchers themselves, funding, and regulations. The interaction between advancing technology and the growing knowledge through universities has an immense impact on the technical capabilities of these alternative models. However, all the actors play a role in this shaping this network, and something like a shift in federal or state funding could drastically affect the utility of these technologies.

Regulatory agencies have a large role to play within this network of alternative models. In the current landscape, their role is largely a barrier. Widespread adoption is limited without regulations in place. These regulations are impacted by human and nonhuman actors including committees such as ICCSVAM, the government, funding, cultural norms, and the validation of these models. The interconnectedness of these actors influences how regulations impact alternative models. As committees continue to push for validation of safety and efficacy and cultural norms shift, the pressure to reform and add regulations increases.

As new alternatives to animal models arise, it is important to consider their ethical implications This can be described by actors such as researchers and their intents, regulating bodies, public opinion, cultural norms, and activist groups. The moral and ethical justification appears to align with the use of alternative models, as it prevents harm to life. However, as these human and non-human actors shape the ethics of alternative models, other concerns in the form of actors can arise. The use of artificial intelligence or sourcing of stem cells will continue to influence and shape the network regarding alternatives to animal testing and introduce new ethical issues.

Ongoing interactions and relationships amongst sets of heterogeneous actors will influence the continuous evolution of alternative methods and models. While the technical

capabilities, regulations, and ethics were discussed as separate entities, they each also have relationships with one another. Furthermore, the system may be impacted by the introduction of new actors, which can alter the network and influence other components. In conclusion, the network of alternative models is a complex social process that is shaped by a variety of factors, human and non-human, that will continue to transform as actors and their relations change over time.

Part IV: The Conclusion

Throughout history, animal models have proven to be a steadfast means of advancing medicine, research, and science as a whole. As a result, animal experiment does not seem to be going away anytime soon. Although their track record is unproven, innovations relating to alternative models have seen exponential growth within the past decades. There have been changes in regulations and a trend toward reducing the use of animal models, however, these approaches are far from a complete substitute for animal experimentation. Over the coming decades, we may see a gradual change as technologies advance and continue to provide evidence of their safety and efficacy.

Within the context of ANT, we can see the distinct networks of animal models and their alternatives, although in reality these networks are connected to one another. Thereby we can see where the networks differ and how those differences may impact the other. In terms of ethics, we can see the stark differences between animal models and alternative models. For the majority of people, the ethical concerns associated with animal experimentation represent a fundamental issue. As society places greater emphasis on ethical considerations, the overall shift supports

humane animal treatment, and alternative models provide a way to mitigate harm. Thus, ethical considerations not only challenge the continued use of animal models but also drive innovation in alternative models, as actors involved in ethical standards strive to find ways to reduce or replace animal use in research.

We can see that the relationships between regulatory agencies and animal models have provided them with a foundation for experimental protocols and procedures that lead to safe and effective drugs and accurate and repeatable research. Regulatory agencies are in the process of developing appropriate protocols and procedures for evaluating the safety and efficacy of non-animal alternatives. As a result, alternative models may face more barriers to acceptance and implementation than animal models, which shows the inhibitory effect of the relationship between regulatory agencies and alternative models. Although regulatory bodies have not yet established uniform guidelines for the utilization of alternative models in research, they are moving towards adopting such models. In the FDA's 2021 Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science report, they outlined their goals to advance towards the 3Rs of animal testing (Commissioner, 2022).

Animal models and their alternatives share a common goal to understand biology through research on diseases, biological mechanisms, drugs, and their effects on the body. However, the means by which this objective is achieved differ significantly. Animal models rely on physiologically similar but distinctly different systems and tissues, whereas alternative models rely on synthetic tissues or materials as well as other means such as computer models. While both these networks share common actors, their roles differ significantly. In the case of alternative models, the work done by animals is translated into technologies such as computer simulations or artificial tissues. Removing animals from research can have significant impacts on

the research process, including changes to experimental protocols, funding requirements, necessary equipment and materials, knowledge of personnel, and the overall technical capabilities of the research being conducted. These differences can make the transition difficult and costly, but their shared objective highlights the importance of ongoing efforts to develop and refine alternative methods and models as they become more accurate and offer a more humane approach to science.

To summarize, we can see the similarities and differences amongst the ethics, utility, and regulatory aspects between animal models and their alternatives using ANT. While there are some commonalities between the two, it is clear that these systems are significantly different and are shifting in very different directions. The future remains uncertain, but in the modern era animal testing is a necessary part of research and a critical piece of medicine. It has also been instrumental in protecting countless people from the adverse effects of drugs. However, advancements in alternative models are gaining momentum. Ethical issues continue to raise more and more questions for animal models, regulatory agencies are continuing to shift towards the 3Rs and adoption of alternatives, and technology has continued to improve and evolve rapidly within fields such as tissue engineering.

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