Innovative Impact of Regulatory Challenges Faced When Transitioning from Animal Testing to Human Clinical Trials

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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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Introduction

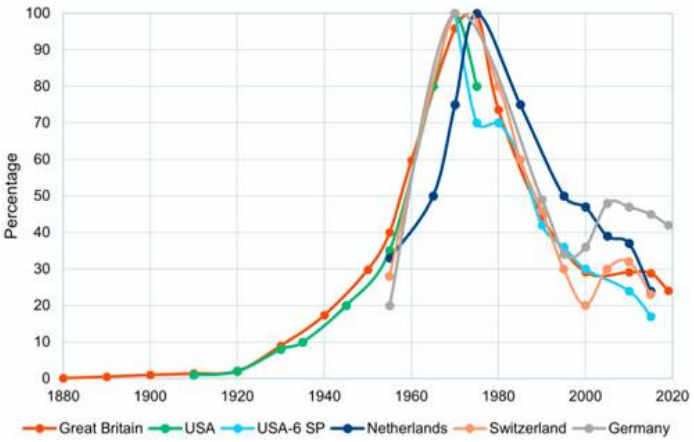
The average medical development process for a single drug takes 10-15 years and costs about $2.6 billion from start to finish (*Research & Development | PhRMA*, n.d.). Before the drug can be brought to market, it must pass numerous stages of preclinical studies in cells and animals, followed by three phases of very rigid human clinical trials. These include first testing healthy volunteers for any general concerns or dangers, followed by a small group of target patients, which provides insight into how the drug will work as it is intended, and finally, a large target patient population to ensure consistent efficacy and safety of the drug. A key step in this process is the use of animal testing in the human drug development process.

For nearly a century now, animal testing has been a staple in pushing a drug through its preclinical development phase, but this idea of animal testing has been around for millennia. Around 350 BCE, ancient Greeks such as Aristotle and Galen, toward the end of the first century, performed animal dissections to study and better understand the intricacies of anatomy and physiology *(Team, 2025*). As the understanding of the human body expanded, so did the experiments. William Harvey conducted experiments using animals in the early 1600s to better understand blood circulation, and by the mid-19th century, Louis Pasteur incorporated animal testing to prove the efficacy of vaccination, followed by Robert Koch, who achieved his title as one of the founders of bacteriology through animal testing. These great successes in animal testing not only resulted in a growing understanding of how diseases interact with the human body but also led to the use of animal testing to develop drugs that fight these, now-understood, diseases (*Franco, 2013*). By the early 1900s, animal testing had significantly increased and soon became a requirement in the United States for all drug and cosmetic development via the Federal

Food, Drug, and Cosmetic Act (FD&C Act) passed by the Food and Drug Administration (FDA) in 1938.

Figure 1

Relative Lab Animal Use in Different Countries (Percentage of Peak Use for Each Country)



Shortly after the FD&C Act, the rest of the largely industrialized world followed suit, resulting in a significant spike in animal testing as seen in **Figure 1**. Here, most industrialized countries relied heavily on animal testing in the 1970s to advance through the preclinical phase of drug development. However, along with this massive surge in animal testing came a growing interest in the ethical implications and concerns of animal testing. In more recent decades, the scientific community has seen a swelling interest in whether animal testing is an ethical and effective method for scientific and drug development. By analyzing diverse evidence concerning the efficacy of animal testing, the ethical implications of harvesting innocent lives, and the use of alternative methods to prove preclinical efficacy, this thesis paper will argue that animal testing is unethical, ineffective, and inefficient, suggesting a need for a more significant shift to new alternative approaches in the medical research community.

Background & Significance

Among many activists and professionals, Dr. William Russell and Rex Burch published "The Principles of Humane Experimental Technique" in 1959. Their book highlights the 3 Rs: *replacement, reduction, and refinement*; the goals of these principles were to minimize pain,

distress, and suffering for research animals while maintaining scientific integrity (*Animal Use Alternatives (3Rs) | National Agricultural Library*, n.d.). *Replacement* refers to utilizing various forms of technology that could take the place of animals in validating a drug. In today's age, especially, researchers are developing numerous technologies and avenues for clinical trials that will replace animal testing. *Reduction* describes a more efficient use of research animals, lowering the amount used through improved experimental design, improved statistical evaluation via more advanced data processing capabilities, and sharing resources/animals between related studies. Finally, r*efinement* emphasizes experimental modifications that eliminate or significantly reduce the animals' pain and improve welfare. This can be done using anesthetics and analgesics, humane animal handling techniques, or environmental enrichment, which improves their well-being.

These concerns grew in the research and ethics communities, eventually gaining traction in the federal government. In 1966, the Animal Welfare Act (AWA) was passed, requiring minimum standards of care and treatment for animals bred for research purposes. However, activists and journalists argue that nearly 95% of animals are not protected by the AWA and that it should be far more inclusive (*Diaz et al., 2024*). In this example, further research into which animals are protected, and to what extent, can provide insight into whether the AWA is sufficient. Further, some authors claim that the AWA, in addition to inefficiently protecting various species, lacks proper enforcement and is often overlooked (*Shook 2022*). Thus, the government's involvement must be further analyzed, including recent revisions to the FDA Modernization Act in 2023, which was originally passed in 2021. Despite these revisions, activists criticize more than just the regulatory statutes intended to protect animal rights. Not only are these legislatures lacking in numerous ways, but the efficacy and cost of animal testing are also challenged. Understanding

why these percentages are so high and what causes these failure rates will motivate subsequent research.

Arguments like these raise questions about why such a high volume of animal-approved drugs fail human clinical trials and whether there might be more effective ways to test their efficacy. A 2018 study found that non-animal methods were more accurate than mouse models when predicting skin sensitization (*Ritskes-Hoitinga, 2022*). While this study only addresses one application of medical research, it exposes the limitations of animal testing and suggests that other avenues be re-examined. Known as New Approach Methods (NAMs), these strategies were developed to develop drugs with a higher success rate, prevent human sickness or injury resulting from unsuccessful clinical trials, and increase the speed of medical innovation approved by the FDA. Currently, the overwhelming reliance on animal testing slows drug development, with an average of 10-15 years for development and up to $6 billion per drug in extreme cases (*MD, 2021*). New advanced technology such as bioprinted organ models, organ-on-a-chip designs, and artificial intelligence can improve the pharmaceutical industry significantly by expediting the drug development process, reducing costs, and improving efficacy. Thus, more research must be done to explore the accuracy of these options and better understand how they can be effectively utilized.

Methodology

Establishing specific methods and techniques for obtaining data is critical to claiming such an argument. Ensuring correct and comprehensive data, such as perspectives, evidence, and key advancements, is critical to successfully establishing and supporting the argument. To ensure a well-rounded evaluation, a multidisciplinary approach will be taken by combining scientific, ethical, and policy analyses of animal testing in the context of drug development. Finally, an STS

approach that presents well-known ethical concepts and theories will be taken to connect all of the arguments.

The first, and most important method used is the review of literature. A variety of literature-based sources, such as scientific studies, ethical arguments, and regulatory policies, will be analyzed to build the main argument and provide supporting evidence. Data on historical and contemporary animal testing practices will be collected, including detailed statistics on drug failure rates, costs, and timeframes for development. Furthermore, the efficacy and ethical impact of regulatory statutes such as the AWA, FDA Modernization Act, and other relevant legislations that affect this area will be assessed.

Two case study analyses will follow, where various research efforts will be presented to highlight how animal testing can lead to failures in drug development and dangerous, unwanted effects during human clinical trials. One explores animal testing and its efficacy in national and international efforts to advance medicine, and the other analyzes how previous tragedies have taught us lessons that have shaped the landscape of FDA and market approval. This thesis will then transition to investigate how new research methods can provide a more accurate, cost effective, and ethical approach to drug development.

To consider NAMS, a comparative analysis will be carried out to compare current animal testing methods to alternative approaches of drug validation for preclinical purposes. This will include factors such as efficacy, reliability, and cost-effectiveness. Discussions surrounding how developed these new methods are and whether they can yet be trusted must be investigated. Cross-examining the predictive accuracy and cost efficiency of NAMs with their barriers to adoption and technical limitations will provide valuable insight into the validity of the claims previously highlighted. Another key discussion will address the 3Rs framework and how that

might be improved with these new research and validation methods. Through these investigations, this research aims to identify the most viable strategies for advancing pharmaceutical innovation in an ethical, efficient, and scientifically robust manner.

Once these main arguments have been presented, two key STS topics and three STS theories will be emphasized and connected to the main thesis argument. The two concepts that will be focused on in this paper are cultural lag and responsible research. Cultural lag is the concept that social norms, values, and institutions move more slowly than technological change (*Team, 2025*). In the context of my STS topic, the slow adaptation of newly developed technology for drug validation will be analyzed. Scientists often get stuck in their ways and prefer procedures they are used to. This paper will explore the transition from animal testing to more ethical drug development methods. The concept of responsible research and innovation addresses how engineers must consider the social realities of their work beyond simply the direct benefits of their work (*Framework for Responsible Research and Innovation*, n.d.). Here, the ethical implications of breeding animals only to be sacrificed for the benefit of human health will be analyzed. The social reality of taking innocent lives, whether they are human or not, must be considered and will be explored in this paper.

The two theories are the social construction of technology (SCOT) and virtue ethics. SCOT will be analyzed from the perspective that technology affects a broader social and cultural context *(Klein & Kleinman, 2002*). From the well-being of other living beings in the animals that are being used to test drugs and therapies, arguments can be made that there are social and cultural consequences in the routine exploitation of animals used for testing. This paper will research these connections and draw educated conclusions that may affect power dynamics between species. A combination of the ethics of care theory and virtue ethics will also be

analyzed, as these are inherently related. Virtue ethics refers to approaching relationships between actors in a system as caring ones and reflecting on what it means to be a good person when making decisions in a larger system (*Rueter, n.d.*). These theories will be explored in the context of our relationships with the animals used for clinical testing. These theories will be further unpacked and analyzed in the context of this relationship.

Literature Review

While animal testing has been a fundamental step in biomedical research and drug development, numerous arguments have arisen against its efficacy and ethical implications. The breeding of animals solely for experimentation is increasingly viewed as inhumane, as it subjects them to suffering and premature death. Meanwhile, the US alone sacrifices over 110 million animals annually, contributing to over 15 million experiments (*Diaz et al., 2024*). Here, the overwhelming sacrifice required to support the US's research and development efforts emphasizes its reliance on animal testing. However, this reliance does not translate to a successful development process. About 64% of NMEs (New Molecular Entities), which are essentially new drugs introduced through research, surpass the animal testing requirements and proceed to the first phase of human clinical trials (*Nine out of Ten Statistics Are Taken out of Context*, n.d.). While removing 36% of drugs unfit for human trials is a good thing, animal lives are wasted on research efforts that either never enter human clinical trials or are sent back to pre-clinical trials only to re-navigate the animal testing process again. In this way, drug development processes can get stuck in a pre-clinical and animal trial cycle that wastes thousands of animal lives without ever producing an effective new drug.

Once a drug gets through animal trials successfully, an alarming 92% fails when translated to human trials (*Vashishat et al., 2024*). With such a strict set of guidelines to be met

during animal trials, this raises questions regarding the efficacy of those results and whether the lives spent to fulfill those guidelines were wasted. The gap in translation between animal and clinical trials can be seen even more severely in cases such as Alzheimer's research, where animal-tested drug trials reach a failure rate as high as 99% after undergoing clinical human trials (*Hutchinson et al., 2022*). Here, there is an inherent discrepancy between the implications that animal trials have on new drugs compared to the results of direct human trials. Thus, the translatability of animal trials to human clinical trials must be questioned.

Two cases, a study of Ethiopian health research, and the thalidomide tragedy, demonstrate the risks of extrapolating findings from non-human models. In Ethiopia, a study was conducted to investigate and identify the challenges of translating animal research to human trials by collecting qualitative and quantitative data from five institutions that strongly contribute to the country's health research (*Abrhaley et al., 2024*). The results of this study found six primary challenges that may contribute to difficulties in translating animal research into human trials. They are presented in Figure 2 below.

Figure 2

A concept map shows themes and sub-themes for challenges that hinder translating animal research into human trials

Despite the study being conducted in Ethiopia, these challenges are broad enough to be applied to any research institution, including those in the US. The graphic highlights the plethora of complications, large and small, that could result in a poor translation to human trials. Specifically, it indicates that genomic and physiological differences between animals and humans lead to poor predictive reliability for drug efficacy and safety. This probable challenge of reproducibility issues very much limits the efficacy of animal trials and is likely a leading cause of high failure rates of human clinical trials. The potential differences between species in disease progression, drug metabolism, and immune response can often lead to misleading results, as seen in the thalidomide tragedy in the mid-1900s (*Kim & Scialli, 2011*). In this example, thalidomide entered and successfully passed animal testing. However, it soon became apparent, about 10

years later that it was a direct cause of severe birth defects in thousands of children, and it was quickly banned in most countries around the world. Animal testing, in this situation, failed to predict the terrible side effects thalidomide would have when used by pregnant women, demonstrating the scientifically flawed method of translating animal testing to human clinical trials. With such a variable process that results in a massive waste of life, efforts must be made to improve drug validation to be more reliable and ethically acceptable.

New drug validation technologies and methods have been created in recent efforts to transition away from animal testing. NAMs (New Approach Methods) present a more ethical and more reliable approach to animal testing. While their comprehensive efficacy must be evaluated further, these technologies offer a promising future for reducing animal testing in drug development. Advancements such as *in vitro* models and organ-on-a-chip technology, 3D bioprinting are quickly gaining traction as more effective and humane alternatives in drug research, and artificial Intelligence (AI) and computational drug models. Recent government legislation has also acknowledged this shift in the approach to drug validation by lifting the requirement that drugs in development must undergo animal trials before human clinical trials begin. The shift in regulation will help end the "needless suffering and death of animal test subjects" and will "get safer, more effective drugs to market more quickly by cutting red tape that is not supported by current science" (*The FDA No Longer Requires All Drugs to Be Tested on Animals before Human Trials | NPR Illinois*, n.d.) This quotation by Sen. Rand Paul, R-KY, emphasizes how effective these alternatives can be in moving away from animal testing.

Recent advancements in numerous *in vitro* models, such as cell culture, organoids, and organ-on-a-chip technologies, are just some of the highly predictive alternatives to animal testing. Cell cultures are the most basic of the three and encompass a wide spectrum of cells,

ranging from tissue-derived primary cell lines to immortalized and reprogrammed cell-derived cultures. In recent decades, 2D models have been the leading cell culture approach, but with the recent development of 3D cell culturing methods, such a nominal approach now offers improved access to key indicators such as soluble factors, nutrients, and oxygen (*Vashishat et al., 2024*). This results in a more accurate representation of cell behavior and drug impact, providing far more accurate and relevant data than any non-human model could. Similar to 3D cell cultures, organoids are 3D structures constructed from a variety of cell types that interact with each other to mimic specific tissue or organ functions. Progressions in stem cell technology and hydrogel-based extracellular matrices have encouraged the improvement of organoid models, enhancing their ability to replicate physiological conditions (*Vashishat et al., 2024*). In this way, these models offer valuable insights into how humans might respond to an NME, both of which are areas animal testing falls short. The third and final notable *in vitro* advancement consists of organ-on-a-chip technology, otherwise known as microphysiological systems or, more informally, as tissue chips. This groundbreaking convergence of microfabrication, microfluidic, and computer advancements has allowed researchers to recreate physiological parameters that influence organ function. Here, scientists now possess a system with the ability to accommodate organized cell and tissue constructs. Thus, these ingenious chips provide the key to significantly enhancing the predictive accuracy of the efficacy and safety of new drugs in human subjects (*Laksanasopin et al., 2009*). Building upon these *in vitro* modeling advancements, 3D bioprinting has recently emerged as another transformative technology that not only refines drug validation methods but also reduces reliance on animal testing.

By creating highly accurate, patient-specific tissue models, 3D bioprinting has unlocked new levels of accuracy when applied to drug validation techniques such as toxicity testing and

drug response. While organoids offer many advantages, as mentioned previously, bioprinting offers more precise spatiotemporal control over the fabrication of human tissue and organ equivalents from scratch that include hollow structures and custom cell types (*Hagenbuchner et al., 2021*). This ability enables researchers to very closely mimic human-like tissue architecture while maintaining direct accessibility to the tissue. While traditional *in vivo* trials require post-operation procedures to extract tissue samples that are then tested, creating a customized organ enables continuous monitoring of tissue-specific physiological drug responses within the printed organ. For example, drug response and toxicity evaluations for the liver require complex, human-cell based models as opposed to animal models due to the species-specific discrepancies in liver metabolism (*Lee et al., 2020*). Here, 3D bioprinting methods were used to construct *in vitro* organ models that sustained liver function (*Goulart et al., 2019*). By manufacturing a more accurate representation of organ function, bioprinting has produced more reliable results and reduced the need for animal testing in this example. Perhaps the most promising advantage of 3D bioprinting is its ability to create reproducible assemblies of tissue equivalents through its use of GelMA, a primary element of synthetic tissues that can be polymerized by UV-light-activated photoinitiators. In combination with these advanced *in vitro* models, computational and AI systems can provide valuable, high-powered analysis.

It is no mystery the immense utility that AI and computational models have in data comprehension and analysis, and over the past few decades, an increase in data collection and automation has paved the way for AI and computational intelligence integration. These models are particularly useful in research areas like disease diagnosis, drug response, and toxicity evaluation, as seen in a recent study that incorporated a deep neural network to identify estrogen mimetics (*Ciallella et al., 2021*). Here, Ciallella et al. introduced AI into their data analysis to

expedite their results and improve the accuracy of their findings. With a quicker, more reliable validation process, researchers will save time and money in their drug development efforts. Thus, AI and computer models in healthcare hold a promising potential to not only revolutionize how drugs are validated and brought to market but also provide a more ethical alternative to animal testing.

Discussion

The shift away from animal testing toward new approach methods (NAMs) can be examined through the lens of cultural lag and responsible research and innovation. Cultural lag is evident in the pharmaceutical industry's slow adaptation to alternatives such as organ-on-a-chip, 3D bioprinting, and AI-driven drug modeling. Despite advancements in these technologies, regulatory agencies and researchers remain reliant on outdated animal models, delaying the full implementation of more predictive and humane alternatives. The Physicians Committee for Responsible Medicine has highlighted the bureaucratic hurdles that hinder the adoption of these technologies, emphasizing the need for institutional change. Additionally, responsible research and innovation demand that scientists consider the broader ethical and societal implications of their methods. By continuing to rely on animal testing, researchers not only perpetuate ethical concerns but also overlook scientifically superior alternatives. As such, integrating NAMs aligns with both ethical considerations and the responsibility to advance science in a way that minimizes harm.

Theories such as the social construction of technology (SCOT), ethics of care, and virtue ethics further support the transition to NAMs. SCOT suggests that technology is shaped by social and cultural influences, and in this case, the persistence of animal testing is maintained by institutional norms rather than scientific necessity. However, as public awareness grows and

regulatory frameworks evolve, NAMs will likely become the preferred standard. The ethics of care theory reinforces this transition by urging scientists to recognize the moral significance of their relationships with the animals used in testing, emphasizing empathy and responsibility in research decisions. Similarly, virtue ethics challenges scientists to reflect on the kind of ethical researchers they strive to be and encourages them to choose methods that prioritize both human and animal well-being. These frameworks collectively illustrate how the shift away from animal testing is not just a technological progression but a necessary ethical and cultural transformation.

Conclusion

The transition away from animal testing toward new approach methods (NAMs) represents a crucial ethical, scientific, and cultural shift in biomedical research. The limitations of animal models, including their poor translatability to human trials and the ethical concerns surrounding their use, highlight the urgent need for more reliable and humane alternatives. The failure rates of animal-tested drugs in human trials, as well as historical cases such as the thalidomide tragedy, underscore the risks of relying on outdated testing methods. As technological advancements such as organ-on-a-chip models, 3D bioprinting, and AI-driven drug development continue to demonstrate superior predictive capabilities, the reliance on animal models becomes increasingly unjustifiable. Furthermore, recent legislative changes acknowledging these advancements signify a growing recognition that drug validation must evolve beyond conventional methods to improve both research efficiency and ethical responsibility.

By examining this transition through the lens of cultural lag, responsible research, and ethical theories such as SCOT, ethics of care, and virtue ethics, it becomes clear that the shift away from animal testing is more than just a scientific necessity. While institutional resistance

and regulatory inertia present challenges, the continued advancement of NAMs provides a viable path forward. As these technologies gain traction, they will not only enhance drug development but also redefine the ethical standards of biomedical research. Moving forward, fostering interdisciplinary collaboration between scientists, policymakers, and ethicists will be essential in fully integrating these innovative alternatives, ensuring a future where drug validation is both scientifically sound and ethically responsible.

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