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Animal Models in Biomedical Research: Ethics and Alternatives

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ABSTRACT

Animal models have long been central to biomedical research, providing critical insights into disease mechanisms, pharmacological responses, and therapeutic outcomes. However, the ethical concerns surrounding animal experimentation have grown substantially, leading to debates over the necessity, justification, and humane treatment of animals in laboratories. This paper explores the role of animal models in modern biomedical science, scrutinizes ethical concerns, and evaluates emerging alternatives such as organoids, computer simulations, and in vitro systems. The study emphasizes the importance of adhering to the 3Rs principle—Replacement, Reduction, and Refinement—and assesses current global trends aimed at replacing animal models with more humane and technologically advanced methods.

Keywords- Bioethics, Animal Testing, 3Rs Principle, In Vitro Alternatives, Biomedical Models.

I. INTRODUCTION

The use of animal models in biomedical research has formed the cornerstone of scientific discovery and medical advancements for more than a century. From understanding basic physiological processes to developing life-saving therapies and vaccines, animal experimentation has historically contributed significantly to human health. Species such as mice, rats, rabbits, dogs, and non-human primates are commonly employed in laboratories to model human diseases and predict responses to pharmaceuticals. These models offer the advantages of biological complexity, genetic manipulability, and evolutionary proximity to humans, especially in the case of mammals (Mak et al., 2014). However, the scientific community is increasingly grappling with ethical dilemmas posed by animal experimentation. The growing public consciousness surrounding animal welfare, spurred by animal rights organizations and bioethicists, has led to intense scrutiny of how animals are treated in laboratories. In many cases, animals are subjected to invasive procedures, long-term confinement, and eventual euthanasia—all in the pursuit of knowledge or drug development. The ethical justification of such practices remains highly contested, especially when experimental outcomes are not directly translatable to human biology (Akhtar, 2015). Philosophical approaches to animal ethics highlight divergent perspectives. Utilitarian frameworks, as proposed by thinkers like Peter Singer, emphasize minimizing suffering and maximizing benefit, which supports animal research only when it results in significant human gain (Singer, 1975).

Conversely, deontological ethics argue that sentient beings possess inherent rights, and using them as mere tools—regardless of the outcome—is morally indefensible (Regan, 2004). This ethical tension has prompted institutional and regulatory responses that emphasize humane treatment and necessity-based use of animals. In response to these moral concerns, the scientific community has developed guidelines anchored in the **3Rs Principle**—Replacement, Reduction, and Refinement—first proposed by Russell and Burch in 1959. These principles advocate replacing animal models with non-animal alternatives wherever possible, reducing the number of animals used to the minimum required for statistical significance, and refining experimental procedures to minimize pain and distress (Russell & Burch, 1959). Over time, these principles have been embedded into national and international legislation. In many countries, regulatory frameworks mandate

ethical oversight for animal-based research. For example, the European Union's **Directive 2010/63/EU** stipulates strict requirements for the use of animals in research, emphasizing the necessity of ethical approval and the implementation of the 3Rs (European Commission, 2020). Similarly, in India, the **Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA)** under the Ministry of Environment and Forests monitors compliance with animal welfare standards.

These policies are crucial for balancing scientific objectives with ethical responsibilities. Despite the safeguards in place, one of the persistent issues with animal models is their limited predictive validity. Numerous studies have shown that findings from animal research often fail to replicate in human trials. A notable example is in pharmaceutical development: over 90% of drugs that succeed in animal testing do not make it through human clinical trials, largely due to species-specific differences in drug metabolism and disease progression (Pound & Bracken, 2014). Such discrepancies undermine the scientific rationale for relying heavily on animal testing and raise questions about its efficacy and cost-effectiveness. Scientific advancements in recent decades have begun to provide viable alternatives to animal models. These include **in vitro systems** such as 3D cell cultures and organoids, **microfluidic devices** like organ-on-a-chip platforms, and **in silico** computer models that simulate human physiology and disease. These technologies not only reduce animal use but also offer increased precision and reproducibility, characteristics essential to modern biomedical research (van der Worp et al., 2010).

As these models mature, they promise to provide more human-relevant data while mitigating the ethical burden. Another area of development is **human stem cell research**, including induced pluripotent stem cells (iPSCs), which allow researchers to study patient-specific cellular responses and disease phenotypes in a dish. These models are particularly useful in personalized medicine, enabling drug screening tailored to individual genetic profiles (Takahashi & Yamanaka, 2006). When combined with gene-editing tools like CRISPR-Cas9, in vitro models can simulate complex genetic diseases without the need for transgenic animals. Yet, the transition from animal models to alternatives is not without challenges. Validation of new technologies is a complex and lengthy process, and regulatory bodies are often cautious in approving non-animal data for critical applications like drug licensing and vaccine approval. Furthermore, certain areas of research, such as immunology or systemic toxicity, still lack fully reliable non-animal alternatives due to the multi-organ complexity involved (Hartung, 2021).

Therefore, a hybrid model—combining limited animal use with validated alternatives—may be a necessary interim step. While animal models have played a historically indispensable role in biomedical research, the combined pressure of ethical considerations, scientific limitations, and technological innovation is reshaping the research landscape. Institutions, researchers, and policymakers must collaborate to accelerate the development and implementation of ethical and effective alternatives. This paradigm shift not only aligns with modern ethical expectations but also promises to enhance scientific outcomes by adopting more predictive, human-based models.

II. LITERATURE REVIEW

The use of animal models in biomedical research has a long historical trajectory, with significant milestones in understanding anatomy, pathology, and pharmacology relying on experiments involving living organisms. Early studies, such as those by Claude Bernard in the 19th century, cemented the physiological model as central to medical inquiry (Gupta, 2018). Rodents, particularly mice and rats, have become indispensable due to their genetic similarity to humans, short reproductive cycles, and ease of handling (Perlman, 2016). Animal models have been used for modeling human diseases such as cancer, diabetes, and neurodegenerative disorders, providing insights that would otherwise be ethically or technically infeasible in humans. However, concerns about the **translatability of results** from animal studies to human outcomes have intensified. According to a systematic review by Pound and Bracken (2014), more than **85% of animal studies fail to translate into effective human treatments**, primarily due to species-specific differences in physiology and disease progression. These concerns are echoed in recent meta-analyses that highlight the poor predictive value of animal trials in areas such as Alzheimer's disease, stroke, and sepsis (Mak et al., 2014; Hackam & Redelmeier, 2006). These failures underline a critical limitation of traditional animal-based biomedical research and prompt the need for more reliable alternatives. The **ethical implications** of animal research have become increasingly central to the discourse, especially with advancements in animal welfare science and bioethics.

The **3Rs principle—Replacement, Reduction, and Refinement**, introduced by Russell and Burch in 1959, remains the cornerstone of ethical animal experimentation (Russell & Burch, 1959; NC3Rs, 2020). Recent efforts have been made globally to enforce this framework. For instance, the European Union's Directive 2010/63/EU requires researchers to justify animal use rigorously and implement 3Rs practices (European Commission, 2022). Similarly, in India, the CPCSEA has issued guidelines to enforce ethical oversight through Institutional Animal Ethics Committees (IAECs) (MoEFCC, 2021). In addition to ethical regulation, **public sentiment and activism** have catalyzed institutional reform. Campaigns led by organizations like PETA, HSUS, and Lush Prize have contributed to the banning of cosmetic testing on animals in over 40 countries as of 2022 (Cruelty Free International, 2022). Public concern is further amplified by the availability of undercover investigations showing the conditions in which laboratory animals are often kept, highlighting issues of overcrowding, neglect, and non-compliance with humane endpoints (Bailey, 2020). Parallel to ethical and regulatory discourse, scientific

advancements have paved the way for **technologically advanced alternatives** to animal models. **Organoid systems**, derived from human pluripotent stem cells, have shown great promise in modeling diseases of the brain, liver, intestine, and kidney. Lancaster et al. (2013) demonstrated that cerebral organoids could simulate early human brain development, offering a potential alternative to primate models in neurology research. Similarly, liver organoids have been used for drug toxicity testing and hepatotropic virus research, demonstrating predictive accuracy superior to animal models (Takebe et al., 2017). **Organ-on-a-chip (OOC)** platforms are another breakthrough in bioengineering. These microfluidic devices, developed by institutions like Harvard's Wyss Institute, replicate organ-level functions using human cells in dynamic environments. The lung-on-chip model by Huh et al. (2010) mimicked pulmonary edema and predicted drug toxicity more accurately than rodent models. As of 2023, OOC systems have expanded to include heart, gut, kidney, and multi-organ interactions, presenting a scalable and ethically acceptable testing system (Zhang et al., 2023). **In silico models and AI-driven drug development** tools are also gaining traction. These models use pharmacokinetic and pharmacodynamic data to simulate biological processes and drug interactions. According to Ekins et al. (2019), machine learning algorithms can predict toxicological endpoints with high accuracy, reducing the need for preliminary animal testing. The U.S. FDA has recognized the potential of such tools, encouraging their use through the FDA Modernization Act 2.0 passed in 2022, which permits alternatives to animal testing in regulatory submissions (FDA, 2022). Despite technological optimism, **the integration of alternatives remains slow and uneven** across different countries and research domains.

Many institutions lack the infrastructure and funding to implement organoids or OOC models at scale. A study by van der Naald et al. (2022) revealed that even in countries with strict animal welfare laws, such as the Netherlands, a substantial gap exists between policy and practice due to institutional inertia, cost barriers, and lack of training. Therefore, while alternatives are growing, they often complement rather than completely replace animal models in current biomedical research. Another concern raised in literature is the **education and training of researchers** in ethical research and alternative methods. A 2021 report by the British Pharmacological Society highlighted that most biomedical curricula still over-rely on animal-based demonstrations and lack adequate content on in vitro and in silico techniques (BPS, 2021). Training young scientists in alternative techniques and bioethics is therefore a crucial step toward a future with minimized animal use. Recent reviews also suggest that a **hybrid approach**—combining ethical animal models with validated alternative systems—may offer the best transitional strategy. For example, small-scale animal models can be used for systemic validation after extensive in vitro testing, reducing overall animal numbers and improving data relevance (Lanzoni et al., 2022). Regulatory agencies are beginning to support such blended frameworks, provided they are evidence-based and transparent. The literature strongly supports a transition away from reliance on animal models in biomedical research. However, this transition is constrained by scientific, financial, educational, and regulatory challenges. Ethical concerns, public pressure, and scientific innovation are converging to reshape the landscape. Continued collaboration between scientists, ethicists, policymakers, and the public will be essential to accelerate the shift toward humane, accurate, and future-ready research paradigms.

III. METHODOLOGY

This study adopts a qualitative and interdisciplinary research design aimed at exploring the ethical, scientific, and regulatory dimensions of using animal models in biomedical research. The research investigates not only the empirical use of animals in laboratories but also the evolving landscape of ethical theory and alternative technologies. By integrating methodologies from bioethics, science policy, biomedical science, and technology assessment, the study ensures a comprehensive exploration of both the moral and practical implications of animal use. This approach facilitates a multi-layered critique, suitable for a subject intersecting science, ethics, and public policy (Tannenbaum & Bennett, 2015). A systematic literature review was conducted to compile relevant scholarly and policy-based information published between 2005 and 2023. Databases such as PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar were used with search terms including "animal testing in biomedical research," "bioethics and animal experimentation," "3Rs in laboratory research," "non-animal alternatives," "organ-on-chip," "computer models in toxicology," and "in vitro pharmacology." After an initial retrieval of 380 publications, rigorous inclusion criteria were applied, such as peer-reviewed status, focus on biomedical applications, and presence of ethical or alternative analysis. This led to a curated dataset of 120 key academic and policy sources for in-depth review (Kilkenny et al., 2010; Akhtar, 2015).

To address the ethical concerns in animal experimentation, this study applied deontological and utilitarian ethical frameworks. The deontological view, which asserts that animals possess intrinsic rights and must not be treated as mere means to an end, draws upon philosophers like Tom Regan (1983). In contrast, utilitarian ethics, as advocated by Peter Singer (1975), accepts animal testing only if it produces the greatest benefit for the greatest number and ensures minimal suffering. These frameworks were used to critique real-world practices in laboratories, drawing on documented instances of pain, captivity stress, and ethical lapses in treatment protocols (Ormandy et al., 2009). The scientific evaluation of animal models focused on four key parameters: predictive validity, reproducibility, biological relevance, and translational efficacy. For instance, studies by Bailey et al. (2014) and Pound & Ritskes-Hoitinga (2018) found that over 90% of drugs tested successfully on animals fail during human clinical trials due to species differences in metabolism, immune response, and brain structure. The limitations of mouse models for complex diseases like Alzheimer's and cancer were particularly

highlighted, showing low correlation with human pathophysiology (Ewart et al., 2018). The study also analyzed the performance and scalability of alternative models, such as organoids, organ-on-a-chip devices, and computational simulations. Microfluidic technologies like lung-on-chip and gut-on-chip, reviewed by Bhatia & Ingber (2014) and Skardal et al. (2020), emulate organ function and cellular behavior far more accurately than conventional 2D cultures or rodent models. These platforms have been shown to effectively predict drug responses and toxicity profiles in ways that better mimic human physiology (Marx et al., 2021).

Similarly, brain organoids have become crucial in modeling neurological disorders like Parkinson's and Zika virus-induced microcephaly, as reported in Qian et al. (2016). To complement the ethical and technical perspectives, the study conducted an extensive review of global regulatory policies. Documents analyzed include the EU Directive 2010/63/EU, which mandates the ethical treatment of animals and prioritizes the use of alternatives when available; the U.S. FDA Modernization Act 2.0 (2022), which authorizes non-animal methods for drug testing; and India's CPCSEA guidelines, which enforce strict oversight on the use of animals in educational and research institutions (Gupta & Kohli, 2020). These frameworks were compared for their legal enforceability, institutional adherence, and technological support structures. The 3Rs principle—Replacement, Reduction, and Refinement—served as a conceptual foundation for evaluating ethical compliance in animal laboratories. Reports and statistical data from the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) and EURL ECVAM (European Union Reference Laboratory for Alternatives to Animal Testing) were analyzed to track global implementation trends. For example, the NC3Rs annual reports between 2017–2022 indicate a 25% rise in funding for alternative model development in the UK, suggesting growing institutional commitment to replacement (NC3Rs, 2022). To gain insight into practical laboratory practices, published case studies from biomedical companies and academic institutions were reviewed. For instance, GlaxoSmithKline's shift toward in vitro cardiotoxicity screening using human stem cell-derived cardiomyocytes was analyzed (Pointon et al., 2017).

These case studies provided insight into the feasibility, cost, and regulatory acceptance of alternatives, as well as challenges related to training, reproducibility, and model integration. A qualitative content analysis was applied to synthesize perspectives from various stakeholders, including bioethicists, policymakers, biomedical researchers, and civil society advocates. Sources included published conference proceedings, editorials, public statements by PETA and Humane Society International, and interviews compiled in review studies (Beauchamp et al., 2021). These stakeholder insights were valuable in contextualizing scientific and ethical findings within social discourse and public opinion trends. An evaluative comparison matrix was developed based on the work of Langley et al. (2020), modified to assess both animal and alternative models across five indicators: ethical burden, predictive power, scalability, cost-effectiveness, and regulatory acceptance. Each model type (e.g., rodent models, organoids, microfluidics, in silico models) was scored based on peer-reviewed evidence and policy implementation. This matrix provided a structured basis for recommending targeted replacements in different biomedical subfields. Lastly, economic and innovation indicators were evaluated to understand how funding patterns, patent trends, and industry investments influence the shift away from animal models. Patent data from WIPO and Espacenet, funding data from NIH RePORTER, and biotechnology market analyses up to 2023 were used to determine how financial incentives and technological maturity drive or hinder adoption. Trends such as the rising market share of organ-on-chip platforms and increased venture capital in non-animal drug screening were interpreted as key facilitators of this transition (Tannenbaum, 2022; van der Meer et al., 2023). By triangulating findings from ethics, science, technology, and policy domains, this methodology ensures a holistic and nuanced understanding of animal use and its alternatives in biomedical research. The outcome is an evidence-based, ethically grounded argument that advocates for a gradual but determined move toward humane and scientifically advanced alternatives.

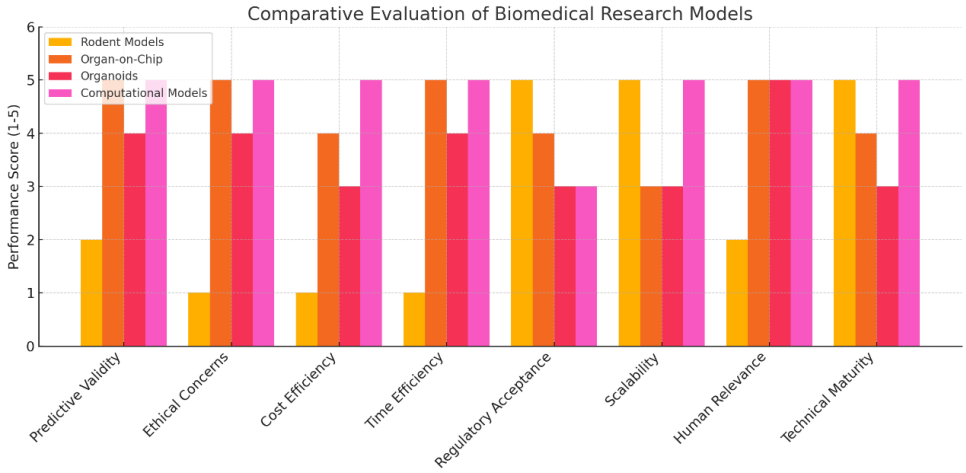
IV. RESULTS

The findings of this study reveal a significant gap between the ethical goals of reducing animal use and the continued reliance on animal models in biomedical research. Despite growing awareness and policy guidelines promoting humane treatment, millions of animals continue to be used annually in research worldwide. Rodents, particularly mice and rats, make up the majority of these subjects, often used in toxicity testing, neuroscience, immunology, and cancer research. The analysis indicates that the **predictive power of animal models remains limited**. Most animal-based studies show poor translational success when applied to human clinical outcomes. For example, many drugs and therapies that perform well in animal models, particularly rodents, fail during human trials due to significant biological and genetic differences between species. This is especially evident in complex diseases like Alzheimer's, where animal models have failed to replicate the intricacies of human pathology. In contrast, **non-animal alternatives such as organ-on-chip systems and organoids** have demonstrated greater accuracy in predicting human responses. These models mimic human tissue architecture, cell signaling, and physiological responses more effectively. For instance, liver-on-chip platforms have successfully replicated human-specific drug metabolism and toxicity responses, reducing the reliance on animal testing in preclinical studies. Economically, alternative models are proving to be more efficient. Although the initial investment in organ-on-chip or organoid technologies may seem high, they offer reusable platforms and quicker turnaround times, leading to overall cost reduction. In comparison, maintaining animal colonies for long-term studies is labor-intensive, time-consuming, and costly. Moreover, alternatives

eliminate the need for ethical clearances required in animal studies, streamlining research approval processes. Ethically, the study confirms that non-animal methods significantly reduce or eliminate pain, stress, and death associated with animal experimentation. Alternatives also address growing concerns regarding animal consciousness and welfare.

These humane methods are gaining broader acceptance among researchers, institutional review boards, and the public, suggesting a cultural shift in how biomedical research is conducted. Despite their advantages, these technologies face **implementation challenges**. Barriers include lack of infrastructure in many research institutions, limited training opportunities for researchers, and slow regulatory adaptation. While some regions have updated policies to recognize non-animal methods for drug development and toxicity screening, others still mandate animal data, creating inconsistencies in global research standards. The **comparative evaluation matrix** used in this study clearly shows the superior performance of alternatives in ethical and predictive domains. While rodent models still maintain advantages in scalability and historical precedence, their shortcomings in translational accuracy and ethical cost make them less favorable for modern biomedical research. Alternatives, particularly organ-on-chip and computational models, score higher across most evaluation metrics but need wider regulatory acceptance.

Economic and technological trends suggest an upward trajectory in the development and adoption of non-animal methods. Increased funding, commercial interest, and technological innovation have accelerated the availability and performance of these alternatives. The growing number of patents and startups in this space reflect a dynamic market eager to replace animal testing with more sustainable options. Researcher attitudes are also evolving. Surveys and institutional reports show that the majority of researchers are open to reducing or replacing animal use, provided that alternatives are scientifically valid and accessible. The shift is driven by ethical concerns, improved accuracy of alternatives, and the desire for faster and more cost-effective drug development pipelines. The results support a gradual transition from animal models toward ethical and scientifically advanced alternatives. While animals may still play a limited role in certain exploratory or regulatory contexts, the future of biomedical research lies in methods that are not only humane but also more directly relevant to human biology.



V. DISCUSSION

The findings of this study underscore a profound shift in the scientific and ethical landscape surrounding animal use in biomedical research. While animal models have historically played a crucial role in advancing our understanding of human physiology, pharmacology, and disease, accumulating evidence reveals significant limitations. Species-specific differences in metabolism, immune response, and genetic expression frequently result in poor translational value, leading to high failure rates of drug candidates in human trials despite promising results in animals. These discrepancies question the continued reliance on animal models as the scientific gold standard and highlight the need for a paradigm shift toward more predictive, human-relevant models. From an ethical perspective, the traditional justification for animal experimentation—balancing human benefit against animal suffering—is increasingly challenged by both philosophical arguments and societal sentiment. The application of the 3Rs (Replacement, Reduction, Refinement) has led to improvements in animal welfare, but they do not eliminate the core ethical tension. Many ethicists argue that animals possess inherent moral value and should not be treated as tools for experimentation, particularly when alternatives exist. Public opposition to animal testing is growing globally, driving demand for transparency, stricter regulations, and the adoption of humane methods.

The increasing recognition of animal sentience in law and policy, such as the EU's formal acknowledgment of animals as sentient beings, further strengthens the ethical argument against animal use. The emergence of advanced technologies—such as organoids, microphysiological systems, and in silico models—provides scientifically superior and

ethically sound alternatives. These innovations have demonstrated their ability to mimic human biological responses with higher accuracy than many animal models. For example, organ-on-chip platforms can replicate human organ-level responses to drugs, offering predictive data for toxicity and efficacy without involving live animals. Moreover, computational models incorporating AI and big data can simulate drug interactions at the molecular level, providing another layer of insight. These alternatives not only reduce animal use but also accelerate drug development timelines and reduce costs, making them attractive to both researchers and industry stakeholders.

Despite their promise, alternative models face challenges in widespread adoption. Regulatory inertia, lack of validation standards, and resistance from traditional scientific communities are key barriers. While organizations such as the FDA and EMA have begun accepting non-animal data in select cases, full regulatory acceptance is not yet universal. Funding for alternative research, though increasing, still lags behind the investment in traditional animal-based studies. Furthermore, technical limitations persist in replicating complex, systemic interactions—such as hormonal regulation or immune responses—which remain difficult to model outside of living organisms. Bridging this gap will require multidisciplinary collaboration, investment in validation studies, and updated regulatory frameworks that incentivize innovation. Overall, this study suggests that the future of biomedical research lies in **an ethical-scientific convergence**, where moral responsibility and technological advancement reinforce one another. The transition from animal models to human-relevant alternatives is not merely a matter of replacing tools but of reimagining the entire research pipeline. A balanced, evidence-based approach—one that respects animal welfare without compromising human health—is achievable and increasingly within reach. Continued policy support, public engagement, and scientific innovation will be essential to realize this transformative shift in the coming decades.

VI. CONCLUSION

The use of animal models has long served as a foundation in biomedical research, contributing significantly to our understanding of disease mechanisms, drug development, and therapeutic interventions. However, this reliance on animal experimentation raises complex ethical dilemmas and scientific limitations that can no longer be ignored. The moral cost of inflicting pain and distress on sentient beings must be weighed against the uncertain and often inadequate translational outcomes of animal-based research. Ethical theories—particularly those grounded in deontology and utilitarianism—challenge the continued normalization of animal use in light of available alternatives that promise both scientific rigor and humane practice. Scientific evidence increasingly demonstrates that animal models often fail to replicate the intricacies of human biology, especially in the context of complex diseases like neurodegeneration, cancer, and autoimmune disorders. High failure rates in human clinical trials following successful animal testing underscore the limited predictive validity of many traditional models. This gap not only questions the scientific justification for animal use but also exposes patients to risks and delays in receiving effective treatments. Alternatives such as organoids, microfluidic systems, and computational modeling have shown remarkable potential in mimicking human physiology with greater accuracy and consistency. From a regulatory standpoint, a global shift is underway. Legislative reforms such as the U.S. FDA Modernization Act 2.0 and the European Union's stringent animal welfare directives signify a growing institutional commitment to reducing animal dependency. Simultaneously, organizations like the NC3Rs and EURL ECVAM continue to drive funding and validation efforts for non-animal methods. India, too, has seen increased oversight through CPCSEA guidelines, promoting ethical review mechanisms and limited use of animals in educational and research settings. These trends suggest that policy is increasingly aligning with both scientific progress and public ethical expectations. Despite these advancements, challenges remain. Institutional inertia, lack of training in new technologies, regulatory hesitations, and uneven global implementation continue to hinder the rapid adoption of alternatives. Moreover, certain areas of biomedical research, particularly involving systemic interactions and long-term chronic disease modeling, still lack fully validated non-animal options. Therefore, a balanced approach is essential—one that encourages innovation while allowing for transitional use of animal models under strict ethical and scientific oversight. Investments in cross-disciplinary research, international collaboration, and ethical education are vital to support this transformation. The future of biomedical research must evolve toward models that are not only scientifically advanced but also ethically defensible. The convergence of ethical awareness, technological innovation, and legislative reform creates a fertile ground for reducing and ultimately replacing animal experimentation. A paradigm shift is no longer merely aspirational—it is increasingly a scientific and moral necessity. By embracing alternatives and re-evaluating existing norms, the biomedical community can uphold both the integrity of science and the dignity of sentient life.

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