**Reducing Animal Testing During Toxicology Testing**

The company seeks to discover and develop new human drugs, a process that involves testing procedures and the use of animals as test specimens. Ethical issues, however, have been raised against the use of animal testing, and individuals and groups are advocating for the non-use or reduced use of animals in toxicological testing of newly developed drugs. The owner of the company is an ethically sensitive people to the use of animals in toxicology testing and he has asked for a minimization of the use of animals during testing. Possible strategies for reducing animal testing during toxicology testing are discussed.

**Solution: Evidence-Based**

The use of effective and efficient research methods and designs is the proposed solution. The existing regulatory guidance and empirical data on the principles of reduction, refinement, and replacement of animal use in toxicology research inform the decision. One of the regulatory guidelines in the European Union, which can affect the market for the company’s developed products in the region, is the need to use scientific tests that do not involve animals (The European Medicines Agency, 2014). The number of animals used in a study, if the usage is necessary, should be minimal but guarantee the fulfilment of test objectives. The guideline also provides for the refinement of the environments in which animals stay before a test study, and the refinement of research methods for the elimination of pain or distress that animals may suffer because of their use in research (The European Medicines Agency, 2014). One of the implications of the guidance is the need to replace animals with alternative tests, unless such a replacement is not possible. The replacement can be achieved through alternative methods such as computer models and in vitro models that simulate the processes that could occur in animals if they were used for tests. The modeling can generate preliminary results for the refinement of the use of animals or can suffice the targeted test goals. Similarly, reliance on data from existing studies and practical considerations of theoretical information can suffice or provide information for refining studies involving the use of animals. The use of modeled results in subsequent and refined tests, which use animals, has the effect of increased validity and reliability and substantiates the need for fewer animals and number of tests for confirmatory results.

The provisions of the guidance for refinement of the environment around animals, before and during a test process, also offer a basis for the reduction of the number of used animals through the principle of refinement. The elimination or reduction of pain and distress, prior to and during a test, has the effects of improving the animals’ physiological condition that is necessary for accurate response to test treatments. Distress and pain, for example, may reduce an animal’s sensitivity to a treatment into undervaluation of treatment effects. Increased effects of the environment to the animals’ sensitivity, however, may lead to overvaluation of the effects of a treatment and undermine the goal of a toxicology test. Improved research methods into high levels of precision also mean the ability to realize acceptable levels of validity and reliability with fewer animals per test and fewer tests. Refinement, therefore, also eliminates the need to use more animals in repeat tests for establishing validity of results. The concepts of reduction, refinement, and replacement of animal usage in toxicology testing, therefore, define strategies for addressing the concern of minimized animal use in toxicology testing (The European Medicines Agency, 2014).

Empirical data supports the significance of methodological refinement in reducing the number of animals used in toxicology research. Methodological and design features of animal test studies influence the minimum applicable number of animals for a satisfactory test outcomes and form a basis for reducing the number of animals in a study (Tornqvist et al., 2014). Data from projects on the reduction of the number of animals in toxicology research illustrates this through a demonstration of a significant effect of applicable reduction measures on the number of used animals. The use of reduction strategies, according to Tornqvist et al. (2014), reduces the threshold number of animals by 53 per cent for rats, 34 per cent for mice, 19 per cent for dogs, and eight per cent for rabbits. Improvements in study methods, based the study by Tornqvist et al. (2014) in which rats were the majority of the used animals, accounts for 68 per cent of the achieved reduction in the number of used animals while improvements in study design account for 20 per cent of the reduction. Tactful coordination of elements of a study is also significant to the reduction of the number of animals in a toxicology research (Tornqvist et al., 2014).

Some researchers may be skeptical about the implementation of practices that pursue the reduction, refinement, and replication principles, while others acknowledge the need to consider minimal use of animals in toxicology research. The cost of using animals in research, and the surrounding ethical issues are some of the factors that researchers are willing to consider, and could lead to such decisions as non-use of animal research and better treatment of animals in research processes (Fenwick, Danielson, & Griffin, 2011). Other researchers, however, are likely to embrace methodological approaches for the reduction of the number of animals per test, if the reduced number promises valid results (Fenwick et al., 2011).

**Conclusion**

The company seeks to discover and develop new human drugs. The processes often require animal testing but there is a need to minimize the number of animals during toxicology testing. The concepts of reduction, refinement, and replacement identify possible approaches for addressing the minimization concern. Improved research methods and favorable environments for animals to be used in tests, which are elements of the reduction and refinement principles, have been associated with accurate and generalizable results and the associated need to use fewer animals for toxicology tests. Use of alternatives to animal tests, such as computer models and in vitro test models can also minimize or eliminate the number of animals in toxicology testing. Empirical results support the effectiveness of research method and design, as well as coordination of elements and activities of research, in reducing the number of used animals in tests. Similarly, the use of alternatives such as read-across other sources, reliance on existing tests, practical consideration of theoretical knowledge, and non-animal approaches have demonstrated, empirically, the significance in minimizing the number of animals in toxicology testing.

**Recommendations**

Evidence exists on the ability to minimize the number of animals used in toxicology research. Validity and reliability of the quantitative studies, and credibility and dependability of the qualitative study are assumed in proposing the solution. The sources contained all the necessary information for establishing the solution. Some toxicology studies do not require the use of animals while others require the use of fewer animals than drug developers may perceive. The use of effective research methods and designs is recommended for ensuring that animals are used effectively and on necessity. The role of preliminary reductionist approaches on the development of efficient and effective research methods and designs, and the role of collaboration with regulatory authorities on understanding the threshold number of animals informs the recommendation. An understanding of alternative methods to animal research and the effectiveness of the methods is also recommended for preliminary studies into the development of focused, effective, and efficient research methods and designs. Read-across options, use of existing test results, practical considerations on theoretical information, computer models, and in vitro models should be the focus of the preliminary studies. All activities in the test processes should also be coordinated for improved test outcomes.

**References**

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 Tornqvist, E., Annas, A., Granath, B., Jalkensten, E., Cotgreave, I., & Oberg, M. (2014). Strategic focus on 3R principles reveals major reductions in the use of animals in pharmaceutical toxicity testing. *Plos One*, *9*(7), 1-11.

**Discussion of the Articles**

**Survey of the Canadian animal-based researchers’ views on the three Rs: Replacement, reduction, and refinement**

The study sought to investigate the views of researchers on the use of the reduction, refinement, and reduction principles in animal research, and associated challenges. The study, following approval by an ethics review committee, used the survey design to collect data. The survey instrument identified participants’ response to questions and rationale behind the responses. Demographic data were analyzed and percentage, a quantitative descriptive statistic, was used to identify participants’ opinions on the use of the reduction, refinement, and replacement in the use of animals in research. Qualitative data analysis was used to develop meanings from the rationale that the participants offered. Question one related to the opinion on the use of animal tissue instead of human tissue. More than half of the participants were indifferent in their responses, and a greater percentage of the remaining respondents justified the use of animal tissues that those who felt human tissues should be used. The second question related to the justification of the use of a given number of animals in a study even if the use of a smaller number could suffice and a majority of the participants justified the use of a higher number. The response to question two would not change if a more expensive animal was used and the cost and ethical issues informed this. A majority of the participants were indifferent on pain management in animal research, though most of the participants expressed willingness. The participants, however, were open to guidance and recommendations are made a role of policymakers in promoting the principles of reduction, refinement, and replacement. Sufficient and diversified sources informed the aim of the study, and these establish novelty and reliability of the study. The results and the discussion sections of the study, with a focus on participants’ perception on the aspects of animal research, were used to develop the solution.

**Guideline on regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches**

The guideline that the European Medicines Agency offered in 2014 identifies existence of regulatory guidelines on the ethical use of animals in research and existence of initiatives and organizations that pursue the objective. New methods are also developed, continually, for refining the involved processes for the reduction and refinement of animal use in research. The guideline applies to test processes for the development of medicinal products for human and veterinary use. It outlines the process of submission and review of proposals for the use of animals in the relevant research areas for the validation of the proposed use of the principles of reduction, refinement, and replacement. The guideline is complementary to the sections one and two of the Directive 2001/83/EC, section three of the Directive 2010/63/EU, and the guidelines for the qualification of novel approaches to drug development. The scope of the principles of reduction, refinement, and replacement are presented, with provision for use of animals on necessity, and refinement of both the test environment and test methodologies. The aim of the principles is the minimization of the number of animals used and the control of pain and distress to which animals are exposed before and during tests. The guideline identifies non-clinical/safety testing during drug development and quality control during manufacturing. The guideline also defines the regulatory scope of the use of the three principles of reduction, refinement, and replacement. The development of the guideline relied on the provisions of other guidelines and recommendations on the ethical use of animals in research. Section four of the guideline, which defines the scope for the regulatory provisions on the three principles, contributed to the solution.

**Strategic Focus on 3R Principles Reveals Major Reductions in the use of Animals in Pharmaceutical toxicity Testing**

The background of the study identifies the incorporation of the concepts of 3Rs in international guidelines, national legislations, and national institutions. The incorporation, however, is not comprehensive and effective. The number of animals used in toxicity research is also high and the study sought to investigate strategies for realizing the 3Rs and the roles and needs of employees whose work revolve around the 3Rs. A retrospective study was conducted on all projects that had sought to improve reduction aspects of the 3Rs in a safety assessment research unit. The improvement initiatives were identified as “improved design,” “improved method development,” and “coordination” (Tornqvist et al., 2014, p. 3) and data was collected on the rate of animal usage before and after each improvement initiative.

The reduction-targeted projects reduced the rate of animal usage by between 8 and 53 per cent for rat, mouse, rabbit, and dog species. The discussion associates methods development with the greatest level of significance in reducing the rate of animal usage, and improved study design and coordination follows it. In addition, Tornqvist et al. (2014) note the significance of process management in organizations and the need to generalize the results from the pharmaceutical industry to other research fields. The ability of the reduction concept, through in silico, in vitro, and in vivo approaches, to reduce animal usage in pharmaceutical research and beyond is concluded.

A variety of sources, including peer-reviewed sources, are used to support the background and discussion sections of the article, and the usage establishes reliability and novelty of the article. The results and discussion sections on the effects of study methods and design on the reduction concept informed the solution.