

Jerald Silverman, DVM, Column Coordinator

Deciding which animals to use

Best Pharmaceuticals had been developing anti-hypertensive drug S-3842, tentatively named Lovartin, and it was now at the stage of toxicological testing in laboratory animals. The researcher completing the IACUC protocol form for the testing procedure wrote that he would be using cynomolgus monkeys as one of the test species because they are considered a standard non-rodent species used in certain toxicological studies, such as the current one. He even provided a literature reference (a standard requirement at Best) to back up the claim. The IACUC diligently reviewed the protocol and eventually approved it.

Dr. Shana Madela, the USDA veterinary officer assigned to inspect Best Pharmaceuticals, was performing a routine inspection and looked through the Lovartin IACUC application. It contained the

statement that monkeys were used because they are “a standard non-rodent species used in toxicological studies and there is a large amount of historical data to support their use.” It also included the reference confirming that statement. Madela understood that monkeys *could* be used, but she was not convinced that they *should* be used. She asked John Scippone, the Attending Veterinarian, if dogs or rabbits could be used as a non-rodent species, rather than monkeys. Scippone responded that the investigator and his team felt that for the needs of the Lovartin study, monkeys were the most appropriate species and that this had been discussed and approved by the IACUC. Nevertheless, Madela was not satisfied that an adequate justification had been provided for using monkeys instead of other non-rodent species, and she cited Best Pharmaceuticals for the oversight.

As expected, the company and its IACUC were infuriated. They felt that it was not within Madela’s authority to question the approval given by the IACUC for the use of monkeys, particularly when the Food and Drug Administration (FDA) had previously accepted their monkey toxicological studies. “Do you know what this means?” said Scippone. “She thinks she has the authority to tell us what species we should use to get approval for a drug. Maybe she should tell that to the FDA. We’ll see how far she gets with that!”

Do you think that Madela was within her authority to cite Best for having what she considered to be inadequate justification for using monkeys? Do you think that the justification provided to the IACUC was sufficient?

RESPONSE

More references required

Heather A. Arrington, RLATG

I think Madela was justified in her concerns and in citing Best Pharmaceuticals. It does not appear that the company did an adequate job of justifying their use of cynomolgus macaques for this research protocol. The company seems to have provided a single reference, which would not be enough rationalization for the use of this species rather than rabbits or dogs in the toxicity studies.

Extensive justification and an exhaustive literature search should be required before using nonhuman primates (NHPs) in a toxicology testing protocol. In the past, there have been many instances of discordances in the data, where results from NHP studies do not match up with results

in humans. For example, several drugs have been reported to cause deaths in humans after studies with NHPs gave no indication that such a result could be expected¹.

The IACUC should have been more proactive in its review of the researcher’s protocol before approving it. Previous approvals from the FDA for a toxicology study utilizing NHPs do not necessarily mean that this study would have been appropriate as well. I also found that Scippone’s comments to Madela seemed vague, and it appeared that he hadn’t taken a hands-on stance himself in assuring that the cynomolgus macaques were an appropriate species for these studies.

The *Guide for the Care and Use of Laboratory Animals*² (The Guide) is very specific about the IACUC’s responsibility to ensure that the proper species and numbers of animals are used for any research protocol. The Animal Welfare Act³ also makes it clear that valid rationalization for any species being used must be documented

and that any IACUC inspection results must be provided to USDA inspectors for review so that they can report deficiencies or deviations and cite those not in compliance.

Best Pharmaceuticals should have a policy requiring the use of more than one reference to justify animal use. This would alleviate further confusion and disagreements pertaining to use of animal species and future citations caused by lack of due diligence on the part of the IACUC and the researchers involved.

1. Bailey, J. Nonhuman primates in medical research and drug development: a critical review. *Biogenic Amines* **19**, 235–255 (2005).
2. Institute for Laboratory Animal Research. *Guide for the Care and Use of Laboratory Animals* (National Academies Press, Washington, DC, 1996).
3. Animal Welfare Act as Amended (7 USC, 2131-2156).

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RESPONSE

More detailed literature review

Jacquelyn T. Tubbs, DVM

Madela was not within her authority to cite Best for inadequate justification for use of cynomolgus monkeys. The *IACUC Handbook*¹ refers to the Animal Welfare Regulations² when justifying the use of animals in an IACUC protocol. The Animal Welfare Act states that a proposal for animal research must include a rationale for involving animals and for the appropriateness of the species. The onus for justifying the species proposed is on the investigator, and it is the responsibility of the IACUC to evaluate the justification. The researcher provided a literature reference as justification for the appropriateness of cynomolgus monkeys. The IACUC reviewed and approved the protocol; therefore, citation by the USDA veterinary officer is not warranted. Madela may disagree with the selection of the animal species; however, her personal opinion cannot legally extend into a citation. As long as the rationale has been reviewed and accepted by the IACUC, and does not infringe on the regulations set by the Animal Welfare Regulations, the protocol does not require the approval of the USDA veterinarian. Also, the protocol meets the requirements of not only the Animal Welfare Regulations, but also those standards set by the *Guide for the Care and Use of Laboratory Animals*³, and the Public Health Service Policy⁴ (in the event that the protocol took place at an institution conducting PHS-supported activities).

Although fault can be found with Madela's decision to cite Best Pharmaceuticals, the justification provided to the IACUC is lacking in depth to support the use of nonhuman primates. A literature review would have been more satisfactory than the single reference that was included in the research protocol. Although the literature reference supports the use of nonhuman primates, evidence has not been offered as to why a species phylogenetically lower

to cynomolgus monkeys could not be used. As indicated in *The Feeding and Caring of an IACUC*⁵, a literature review should be able to answer the following questions: What databases were used to gather information? What dates were covered in the literature search? What other standard non-rodent species were researched? What are the disadvantages in using an alternate animal species, and how would these affect potential experimental results? The preceding questions are common inquiries that can be answered by a literature review, and not a literature reference supporting the decision of the investigator. A more detailed literature review helps the IACUC to make a more fully informed decision when reviewing protocols using higher animal species. This would benefit the institution when site visits occur and questions are asked, such as those asked by Madela. Additionally, the IACUC should consider re-evaluating its protocol to determine whether the appropriate questions are being asked of the researcher. This would allow the IACUC to obtain complete information pertaining to research proposals.

The concern Madela expressed over the Lovartin IACUC application was valid, even though her subsequent actions were unauthorized. The USDA does not have the authority to cite an institution for its selection of an animal species for research. However, an institution should have a sufficient explanation available for site visitors that may raise the same questions.

1. Spinelli, J.S. Justification for the use of animals. in *The IACUC Handbook* (Silverman, J., Suckow, M.A. & Murthy, S., eds.) 149-151 (CRC Press, Washington, DC, 2000).
2. Animal Welfare Act and Animal Welfare Regulations. 9 CFR, Chapter 1, Subchapter A. §2.31, e.2.
3. Institute of Laboratory Animal Resources. *Guide for the Care and Use of Laboratory Animals* (National Academies Press, Washington, DC, 1996).
4. Public Health Service. Policy on Humane Care and Use of Laboratory Animals. (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
5. Kreger, M.D. The literature search for alternatives. in *The Feeding and Caring of an IACUC* (Podolsky, M.L. & Lucas, V.S., eds.) 139-153 (CRC Press, Washington, DC, 1999).

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RESPONSE

Adequate justification needed

Steven M. Kuhlman, VMD, DACLAM & Alyssa McIntyre, DVM, DACLAM

It appears that Scippone has misinterpreted the citation. Madela cited Best Pharmaceuticals for a lack of justification for use of cynomolgus monkeys. This is not a citation for using the wrong species altogether. The USDA may not tell a pharmaceutical company what species should be used. The Animal Welfare Regulations¹ specifically address the need for a proposal to contain a rationale for the appropriateness of the species to be used in a study. Because testing prospective drugs on animals is necessary for safety assessment according to the Food and Drug Administration, regulations are often cited as to the appropriateness of the non-rodent species. These regulations do not actually define which specific species are to be used. The IACUC proposal should specify why the monkey is the appropriate animal model rather than simply confirming that a non-rodent species must be used. A different species may be a better model for toxicological testing of an anti-hypertensive drug. The decision to use a particular species should be based on species anatomy, pharmacology and physiology and on the biochemistry of the drug being developed.

Russell and Birch developed the 3Rs², which are often used as the basis for decisions on animal use and welfare issues. Included in these principles is the use of a phylogenic perspective to choose an appropriate animal model for a study. Nonhuman primates are placed at the top of that phylogenic tree; therefore, special scientific justification should be expected when the use of this animal is proposed in a study. Whenever a species of lower phylogeny might be used, it should be. The Food and Drug Administration requires the use of a non-rodent species, often the dog or monkey because of similarities to specific human biochemical pathways.

Non-rodent animals considered standard models for toxicology studies include rabbit, dog and monkey, specifically the

New Zealand White rabbit, the beagle dog and the cynomolgus monkey. Because these animals have been traditionally used, there is substantial accumulation of historical data. Given this extensive historical data, there is some concern that use of a different animal model could delay approval of a new drug—even if another animal is a better model. It is unfortunate that the idea that ‘we have always done it this way’ becomes more important than the scientific reality of which animal is most appropriate as a model. A statement confirming that there is a large amount of historic data to support the use of a specific animal may be included, but it should not be the sole basis for justification.

Laboratory animal veterinarians are trained to identify appropriate animal models and should be consulted when a proposal is being developed. As veterinarians, we owe it to the animal and the study to use our education and training to support the best science. That fact that we have always done studies one way or another does not mean that is the best way. Adequate justification for the use of any animal, be it rodent or non-rodent, should be provided in all protocols. Inclusion of a specific justification and an accompanying literature search utilizing appropriate terms might have convinced Madela and prevented the citation.

1. Animal Welfare Act and Animal Welfare Regulations. 9 CFR.
2. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen and Company, London, 1959).

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A word from USDA, FDA and OLAW

In response to the issues raised in this scenario, the United States Department of Agriculture, Animal and Plant Health Inspection Service, Animal Care (USDA/APHIS/AC), the Food and Drug Administration (FDA) and the Office of Laboratory Animal Welfare (OLAW) offer the following clarification and guidance:

The Animal Welfare Act and regulations (AWR) and the PHS Policy require research facilities to ensure that procedures involving animals will avoid or minimize discomfort, distress and pain to the animals^{1,2}. Toxicological studies are considered research procedures that may cause more than slight or momentary pain or distress to the animals involved. As such, the principal investigator must consider alternatives (e.g., replacement with a species of a lower phylogenetic order or using alternative methods as suggested in FDA test guidance documents regarding the use of *in vitro* methods). The written narrative description of the methods and sources used to determine that alternatives were not available must be provided to the IACUC¹. In non-clinical studies, FDA may provide guidance on the use of rodent and non-rodent species in toxicological evaluations. When determining the appropriateness of a non-rodent species, consideration should be given to selecting a species of the lowest phylogenetic order that will yield the most informative data.

The rationale for involving animals, and the rationale for the appropriateness of the species to be used, as required in each research protocol by the AWR and the PHS Policy, may be developed from the information gathered in the search for alternatives^{1,2}. This detailed explanation enables the IACUC to ensure that animal pain and distress are minimized, unless otherwise scientifically justified. It is the IACUC’s responsibility to review and confirm that a sound, objective and logical reason has been provided for each of these required elements prior to approving the use of animals for the research proposal³.

The USDA inspector has the authority and duty to enforce the Animal Welfare Act and the regulations. Any noncompliant item could result in an inspection report citation, with further action taken as warranted.

1. Animal Welfare Act and Animal Welfare Regulations. 9 CFR, Chapter 1, Subchapter A – Animal Welfare: Part 2 Regulations. §2.31(d)(1)(i-ii) and §2.31(e)(2).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* IV.C.1.b. and IV.D.1.b. (US Department of Health and Human Services, Washington, DC, 1986; amended 2002).
3. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals – Frequently Asked Questions*. Protocol Review, Question No. 7. (US Department of Health and Human Services, Washington, DC, 2006; revised 2008). http://grants.nih.gov/grants/olaw/faqs.htm#proto_7.

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