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 expected[1].

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 Act[3] 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).

Arrington is the In Vivo Drug Efficacy Study Director at Taxolog, Inc., Tallahassee, FL.