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Validated alternatives: is immediate implementation required?

Martex Research and Development was an up-and-coming force in the pharmaceutical industry betting on the success of Baluride, its first injectable monoclonal antibody. As required by federal regulation, the company tested each lot of final containers of Baluride for pyrogenic (fever-causing) substances by intravenous injection of Baluride into rabbits. For the Martex IACUC, this was almost a routine procedure considering the number of times the Committee had approved this test. There were no reported problems and after its initial approval, the IACUC did not revisit the specific activities under that protocol apart from the annual USDA-mandated protocol review.

About two years after the IACUC approved the rabbit pyrogenicity test for Baluride, Martex (following federal specifications) validated the Limulus Amebocyte

Lysate test (LAL) for Baluride as an alternative to the use of rabbits. The company subsequently had its product license properly amended to use either the LAL or rabbit test. Martex and its legal team decided to continue with limited rabbit testing for a short time longer, concurrent with the use of the LAL, until the company could be fully assured that there would be no regulatory, technical, or legal problems from switching mid-production to the LAL.

None of these activities were of particular concern to the Martex IACUC, which simply assumed that upper management's decision was appropriate and binding. However, as could be expected, the word spread about the Martex IACUC's approval of the LAL for Baluride. When that happened, various animal rights groups in the area demanded that Martex immediately abandon all rabbit

pyrogenicity testing for Baluride. Martex was in a quandary as to the best way to react. While this was being debated within the company, the animal rights groups contacted the USDA, demanding that the USDA enforce §2.31(d)(1)(ii) of the Animal Welfare Act regulations (AWARs), which they said required Martex to use the LAL because it was an available and now validated alternative to the use of rabbits and would replace a potentially painful or distressful procedure.

If you were a member of the Martex IACUC, would you agree that the LAL test should be immediately substituted for all Baluride rabbit pyrogenicity testing? Does the IACUC or the USDA have the authority to make such a demand on the company, apart from the normal protocol review process?

RESPONSE

Baluride: don't get taken for a ride

Greg Stickrod, MS, LATG

The goal of every pharmaceutical company is to get a product to market. Therefore, it is reasonable to expect that Martex would be excited to get their antibody, Baluride, to this stage. The legal team and upper management want to safeguard their product. Validation of a new test may mean one thing to one agency and something different to another. Upper management would have justifiable concerns that satisfying a requirement of one agency could put them in jeopardy with another agency.

Everyone wants alternatives to animal testing, and there are several good reasons for this. The most obvious reason is the humane concern for the animal. But time and cost are also considerations. *In vitro* tests can be less expensive and less time consuming than using live animals. So there are compelling reasons, at all levels, to replace the use of live animals with the LAL test as soon as possible.

The IACUC erred when it accepted the judgment of upper management without question. It is the responsibility of the Martex IACUC to review the use of animals according to USDA regulations which state that "[p]roposed activities and proposed significant changes in ongoing activities that have been approved by the IACUC may be subject to further appropriate review and approval by officials of the research facility. However, those officials may not approve

an activity involving the care and use of animals if it has not been approved by the IACUC¹." The IACUC should have reviewed these protocols without consideration for the decisions of upper management.

With appropriate justification the IACUC could approve the use of rabbits for pyrogen testing while the alternative test is being used in parallel. The scientific/technical justification and regulatory concerns should be clarified in detail in the protocol application. Scientists submitting the protocol could request parallel testing until they are satisfied that there are no scientific/technical problems with the alternative test, and that it will be accepted by all regulatory agencies.

1. 9 CFR Subchapter A—Animal Welfare, §2.31(d)(8).

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