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United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

Center for Veterinary Biologics

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CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 12-12

TO: Biologics Licensees, Permittees, and Applicants
Veterinary Services Management Team
Directors, Center for Veterinary Biologics
Deputy Administrator, Animal Care

FROM: Richard E. Hill, Jr. */s/ Richard E. Hill, Jr.*
Director
Center for Veterinary Biologics

SUBJECT: Use of Humane Endpoints and Methods in Animal Testing of Biological Products

I. PURPOSE

This Notice informs licensees, permittees, and applicants of current Center for Veterinary Biologics (CVB) policy concerning the use of humane endpoints in animal challenge tests and the use of anesthesia before and during intracerebral (IC) inoculation. It confirms CVB's commitment to replacing, reducing, and refining animal use.

II. BACKGROUND

Title 9, Code of Federal Regulations (9 CFR), Part 117.4(e) indicates that animals used in testing of biological products may be treated or humanely destroyed if illness has progressed to a point where death is certain to occur. The definition of that point (the humane endpoint) is to be specified in the Outline of Production. This Notice clarifies the humane endpoint for all animal challenge potency tests codified in 9 CFR 113, provides guidance on establishing humane endpoints for potency tests that do not follow those standard requirements, and provides for the use of anesthesia for IC inoculation of mice for inactivation and potency testing.

III. POLICY

All codified potency tests (with the exception of the rabies challenge test discussed below) that are conducted by administering viable virus, bacteria, or a bacterial toxin to animals in a dose that is expected to be lethal should be modified (in the Outline of Production) to include the following wording, unless justification for alternative wording acceptable to the CVB is provided:

> Moribund animals exhibiting clinical signs consistent with the expected disease pathogenesis that are unable to rise or move under their own power should be

> humanely euthanized and considered as deaths as outlined in 9 CFR 117.4. Observations must be made with sufficient frequency to ensure suffering is minimized.

In the case of the rabies challenge described in 9 CFR 113.209, 9 CFR 113.312, and Supplemental Assay Method 308, acceptable wording is:

> Animals exhibiting paresis, signs of paralysis, and/or convulsions must be humanely euthanized and considered as deaths as outlined in 9 CFR 117.4.

Similar definitions should be incorporated into non-codified potency and safety tests and efficacy study protocols. Proposed endpoints will be reviewed on a case-by-case basis.

When implementing humane endpoints, equal treatment must be given to both vaccinated and control animals. Criteria should be as objective as possible, to minimize differences in individual interpretation. Observations must be documented and support euthanasia based on humane endpoint criteria.

Firms are strongly encouraged to use anesthesia for IC inoculation of mice when conducting rabies vaccine inactivation testing under 9 CFR 113.209(d)(2)(i) and for IC inoculation with challenge virus for potency testing under 9 CFR 113.209(d)(3). Firms wishing to use anesthesia in such testing should contact their Reviewer.

Care and attention, including training and procedures, must be used to ensure that the anesthesia is performed in such a way as to minimize pain and suffering.

The CVB encourages the use of analgesics in animal studies and potency testing, when it can be shown this does not affect the study outcome.

Additional policy and guidance is currently under development.

IV. IMPLEMENTATION/ APPLICABILITY

This change is effective six months from the date of this Notice.

In implementing the requirements of this Notice, firms are strongly encouraged to use the following references, as applicable:

Supplemental Assay Methods, including 308, 613, 624, 625, 626, and 627,

The references cited on the “Human Endpoints and Euthanasia” website maintained by USDA’s Animal Welfare Information Center, and

Appendix 2 of the Report and Recommendations of the European Centre for the Validation of Alternative Methods (ECVAM) Workshop 48.