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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Dear Dr. Hill,

I appreciate having had the opportunity to speak with you and Dr. Geetha Srinivas at the ICCVAM conference in September. In light of information presented at that workshop, I would like to ask for specifics regarding the Center for Veterinary Biologic's (CVB) approval process for manufacturers seeking to use supplemental assay method (SAM) exemptions rather than challenge-based potency tests for vaccines. I am also seeking clarification regarding CVB's role in supporting refinement opportunities for the poultry Newcastle Disease Virus (NDV) vaccine.

CVB approval of manufacturers' use of SAMs

Through its SAMs, USDA appears to allow the use of assays that refine or replace the use of animals in experiments by exempting manufacturers from codified *in vivo* assays. According to SAMs 624, 625, 626 and 627 (all of which are pending standard requirements), exemption from Leptospira bacterin challenge testing apparently requires that vaccine manufacturers satisfy the "Requirements for a valid assay" and "Requirements for a valid test bacterin" specified therein. However, information obtained through a Freedom of Information Act request regarding an investigation of one leptospira vaccine manufacturer noted that the facility sent samples of its master seed cultures for several Leptospira serovars to CVB for approval prior to using these SAMs. The failure of this company's seed lots to pass CVB's approval process is cited BY WHOM to explain the company's inability to qualify for the exemption from challenge testing provided by these SAMs.

We would appreciate your confirming that seed lot approval is indeed a necessary prerequisite for the use of SAMs 624—627? If that is case, please let us know the tests that CVB conducts in order to determine the suitability of a manufacturer's Leptospira serovars for use in these SAMs. Does CVB require similar submissions and subsequent approval for the use of other SAMs? For all SAMs, is the submission of information or materials to CVB seeking exemptions in order to use SAMs considered confidential business information?

NDV vaccine potency test refinement opportunity

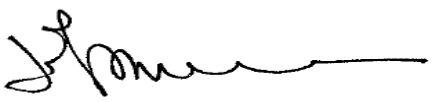
At the ICCVAM workshop, Dr. Srinivas spoke about potential strategies for replacing the use of the vaccine challenge potency test for several poultry vaccines, including NDV vaccines. Noting that no additional animals would be required to build a correlation to the challenge approach currently required 9 CFR 113.205, Dr. Srinivas noted that correlation to either a serological refinement or to an *in vitro* replacement "would be straightforward."

Both serological refinement and *in vitro* replacement methods have been described in the literature, and both have been implemented for regulatory use outside of the United States. An *in vitro* replacement for the NDV vaccine challenge method is described in the current European Pharmacopoeia 7.0, and was first included in monograph 0870 in 2008 alongside an existing serological method. During the validation study leading to the inclusion on the *in vitro* method, 14 laboratories analyzed nine vaccine batches from multiple manufacturers and demonstrated that the antigen content of each vaccine could be determined "with high precision" using ELISA[1]. High correlation was demonstrated between the results of the ELISA-based potency assay and the results of the serological potency assay (monograph 0870, method A), in addition to strongly correlating with clinical protection in vaccinated chickens after challenge with virulent NDV. Each of the participating laboratories concluded that the ELISA assay precisely and reproducibly measures NDV vaccine batch potency. "In this respect," the validation study authors note, "the [ELISA] method can be regarded as superior to the older, more variable methods."

Considering CVB's stated position on the relative ease of conducting a collaborative study to correlate the existing challenge-based potency test with either serological or fully *in vitro* replacement assays, and considering the demonstrated strengths of the use of an ELISA-based NDV vaccine potency assay, does CVB accept results of this *in vitro* assay in place of the *in vivo* potency assay outlined in 9 CFR 113.205? If not, would CVB host a similar collaborative study among U.S.-licensed NDV vaccine manufacturers?

In addition to outlining CVB's process for approving the use of SAMs, please let us know what we can do to facilitate CVB's efforts to promote any strategy to bring NDV vaccine potency testing refinements or replacements closer to regulatory acceptance and use. Please do not hesitate to contact me directly at (323) 437-8003 or via email at JeffreyB@peta.org regarding these important matters and I look forward to hearing from you on these important matters at your earliest convenience.

Sincerely,



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[1] Claasen I. et al. 2004. Validation study to evaluate the reproducibility of a candidate *in vitro* potency assay of Newcastle Disease vaccines and to establish the suitability of a candidate biological reference preparation. Pharmeuropa Bio 2004-1; 1-14.