Environment, Health and Safety
DIVISION OF FACILITIES PLANNING & MANAGEMENT
UNIVERSITY OF WISCONSIN–MADISON

To: National Institutes of Health Office of Science Policy

From: The University of Wisconsin-Madison Institutional Biosafety Committee

Re: Proposed changes to the *NIH Guidelines*

Date: October 6, 2023

We are writing to provide comments on the proposed amendment of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*, Federal Register Document Number 2023-17178, on behalf of the University of Wisconsin-Madison Institutional Biosafety Committee (IBC).

In general, the UW-Madison IBC does not take issue with any of the proposed changes to the *NIH Guidelines*. However, as drafted the proposed amendment is a missed opportunity to make additional changes that would significantly improve the effectiveness of the *NIH Guidelines*. We propose that the NIH Office of Science Policy consider two additional changes not currently included in the proposed amendment.

First, we propose that Section III-D-4 be amended to remove the requirement that the minimum containment level for any recombinant microbe being administered to any whole animal be set at BL2/BL2-N (BSL2/ABSL2). The administration of microbes that are risk group 2 and higher to animals already have minimum containment levels set under Section III-D-1, so this requirement only impacts the administration of recombinant risk group 1 microbes to animals. In practice, this means that Minor Action requests under Section IV-C-1-b-(2) must be submitted to request approval to perform what is often very low risk research at BL1/BL1-N (BSL1/ABSL1). This creates an unnecessary adminstrative burden without any improvement in safety. This proscriptive approach also goes against the entire premise of risk assessment upon which the *NIH Guidelines* are meant to be based. We propose instead that the IBC be allowed to set containment levels for recombinant risk group 1 microbes administered to animals according to their assessment of the risks associated with the microbe, specific recombinant modifications, and animal species involved.

Second, we propose that the *NIH Guidelines* be amended to address a barrier to veterinary animal research. Under the *NIH Guidelines*, research animals receiving recombinant materials may not be released unless approval has been granted by another federal agency with jurisdiction. This means a client-owned animal that is participating in a research study cannot go home again if it receives recombinant materials. While it is important to prevent the release of experimental recombinant materials and organisms into the environment and wild populations, this prohibition effectively disallows clinical trials with client-owned animals that are not actively regulated by the FDA or USDA. Importantly, this excludes animal clinical trials not intended for the development of human therapeutics that are not directly involved in commercialization of an animal biologic. These exclusions include proof of concept studies for

the development of animal therapeutics and compassionate use of experimental biologics in animals.

NIH employees have publicly acknowledged the "regulatory dead zone" created by the gap between the *NIH Guidelines* and what falls under the jurisdiction of other federal agencies, yet it is not clear that any steps have been taken to address this problem. Meanwhile, institutions that receive federal funding and are subject to the *NIH Guidelines* cannot participate in these studies. This excludes universities with robust veterinary and agricultural schools – often those best poised to successfully conduct such studies – from conducting important research that serves to protect and treat our pets, service animals, and livestock.

Examples of instances where UW-Madison researchers came up against this barrier include the compassionate use of a therapeutic melanoma vaccine for cancer treatment in dogs and compassionate use of experimental poultry vaccines to protect domestic falcons during an avian influenza outbreak. In some instances we have been able to work with other federal agencies to obtain clearances, but in other instances the process of navigating the gaps in jurisdiction became so arduous and time-consuming that the researchers withdrew, the studies never proceeded, and the potential benefits to domestic animal populations were lost.

This "regulatory dead zone" is created by the limiting language in the *NIH Guidelines* and could be addressed by amending the *NIH Guidelines* to specifically allow the use of client-owned animals for veterinary clinical trials with recombinant materials. We propose that a section be created to cover veterinary clinical trials involving client-owned companion, service, and agricultural animals. This new section would be analogous to Section III-C, which covers human clinical trials with recombinant materials. Section III-C sets a precedent for living subjects of research with recombinant materials that are not subject to containment or prohibition of release. As with human clinical trials, the potential for recombinant materials and organisms used in veterinary clinical trials to be released into the environment (e.g., through shedding) would be part of the risk assessment performed by the IBC prior to approval to ensure effective precautions are used to prevent exposure to the community or wild populations.

Thank you for your consideration.

Sincerely,

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