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Federation of American Societies for Experimental Biology

Representing Over 130,000 Researchers

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Office of Laboratory Animal Welfare (OLAW)
National Institutes of Health
RKL 1, Suite 360, MSC 7982
6705 Rockledge Drive
Bethesda, MD 20892-7982
Attn: Patricia Brown, VMD, MS
olaw@nih.gov

RE: NIH Request for Information: Animal Care and Use in Research (NOT-OD-18-152)

Dear Dr. Brown:

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to comment on the Request for Information on ways to improve the coordination of regulations and policies with respect to research with laboratory animals as required by the 21st Century Cures Act (Cures), Section 2034(d). FASEB is a coalition of 30 life science societies representing more than 130,000 biological and biomedical researchers, many of whom are involved in the humane care and use of animals in research and education. Congress, through the passage of Cures, and the Administration, through its reference to accumulated regulatory burden in the President's Management Agenda: Modernizing Government in the 21st Century, recognize that it is essential to take a comprehensive approach to eliminate duplicative, outdated, and unneeded regulatory requirements.

Many of the comments in our response are derived from Reforming Animal Research Regulations: Workshop Recommendations to Reduce Regulatory Burden[1]. These recommendations are the result of a coordinated effort organized by FASEB, the Association of American Medical Colleges, the Council on Governmental Relations, and the National Association for Biomedical Research, which brought together university investigators, laboratory animal veterinarians, and administrators engaged in animal research or oversight; chairs and administrators of Institutional Animal Care and Use Committees (IACUCs); directors of university animal welfare programs; accreditors; and representatives of associations with members who are engaged in animal research and oversight.

[1] http://www.faseb.org/Portals/2/PDFs/opa/2017/FASEB-Animal-Regulatory-Report-October2017.pdf

This report was timely for a number of reasons. Over the past thirty years, the regulatory environment has not kept pace with the advances in science or animal care. Today's new technologies allow for better data and less animal stress. Knowledge about animal care continues to expand. In addition, training in animal care has increased dramatically. Taking this into account, the overarching goal of the workshop was to identify specific, actionable recommendations for promoting regulatory efficiency, animal welfare, and sound science that the NIH, USDA, and FDA could use to reduce burden to investigators and universities. The guiding principle was that no recommendation would compromise animal welfare.

Input is sought on each of the following proposed actions that the agencies are considering:

1. Allow investigators to submit protocols for continuing review using a risk-based methodology.

FASEB believes that allowing investigators to submit protocols for continuing review using a risk-based methodology is a good start; however, it does not go far enough. Risk-based methodology should be used for all protocols whether new or continuing.

Human research regulations already allow for the use of risk-based approaches to evaluate human subjects protocols. Some forms of human subjects research have been designated exempt and others qualify for expedited review by a single member of the IRB, with no requirement to secure agreement from other members.

Extending this practice to animal research is beneficial two-fold: it allows for enhanced animal welfare by focusing on research that may present a higher risk for pain and/or distress and allows investigators to devote more time to research. It would also mean that studies with little risk could be processed more expeditiously. In sum, this risk-based approach is more administratively efficient than the current animal regulatory framework and still maintains necessary protections.

Therefore, FASEB recommends that all protocols whether continuing or new be reviewed using a risk-based methodology. OLAW could amend the protocol review requirement to define types of studies involving low-risk, noninvasive, or minimally invasive procedures. These studies could then be deemed exempt from full IACUC consideration or eligible for administrative or designated member review (DMR), without concurrence by the full IACUC (expedited). This would be consistent with how human subjects research is reviewed.

2. Allow annual reporting to OLAW and USDA on the same reporting schedule and as a single report through a shared portal.

A recommendation made in the 1999 NIH Initiative to Reduce Regulatory Burden[2] suggested that there be one common form in which to report pertinent information annually. It stated that, "… coordination among the three organizations [included AAALAC International] could likely yield a common report that would reduce duplication and overlap while satisfying the needs of all three organizations." FASEB concurs that there should be one common form for OLAW and USDA annual reporting with information collected on the same schedule. This would allow organizations and their IACUCs to gather relevant information on the same timeframe thereby reducing administrative burden. However, without changing what is collected in each report, the effect may have limited impact on reducing burden.

We suggest that only Animal Welfare Act (AWA) category E animals be required in the USDA annual report. The classification of pain categories for AWA regulated animals significantly adds to regulatory burden without providing an accurate metric for animal welfare. A retrospective calculation of the number of regulated animals used in each category (in contrast to proposed) significantly adds to the time and effort needed to report each year. This does nothing to enhance animal welfare as the animals have already been involved in a research protocol.

Reporting on the other categories of animals (including those being bred, conditioned or held for research) does little to educate the public on efforts to reduce the number of animals in research. Many factors, including federal research budgets, research aims, and public health emergencies, can affect animal use numbers year over year. Thus, FASEB believes that instead of using the time of the animal care staff to collect exact numbers of animals, they could spend that time directly caring for the research animals.

A series of check boxes for OLAW annual report requirements would also serve to reduce administrative burden. For example, instead of requesting the dates for institutions' semi-annual program evaluations and facility inspections, a simple checkbox could indicate that such evaluations took place. Likewise, a checkbox indicating that the IACUC is in good standing comprised of the required members set forth in PHS Policy would be beneficial.

[2] https://archives.nih.gov/asites/grants/06-17-2015/archive/grants/policy/regulatoryburden/animalcare.htm

Finally, we would recommend that information satisfying each of the agency's requirements only go to that respective agency. For example, numbers of Category E animals should only be transmitted to USDA, not NIH.

Some of these changes may require an update to the Animal Welfare Regulations and/or PHS Policy, but we encourage USDA and OLAW to take every necessary step to reduce excess burden that does not serve a purpose in advancing animal welfare.

3. Harmonize the guidance from NIH and USDA to reduce duplicative considerations of alternatives to painful and distressful procedures.

The Federation agrees that harmonizing guidance from NIH and USDA on considerations of alternatives to painful and distressful procedures would be useful. However, it will only benefit the regulated community if the guidance adheres to the language and intent of AWRs and not USDA's Animal Care Policy #12.

Section 2.31(d)(1)(ii) of the AWR requires the IACUC to determine whether proposed animal use activities meet various requirements, including verification that the principal investigator "has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, used to determine that alternatives were not available."

USDA's Animal Care Policy #12 states that "APHIS continues to recommend a database search as the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures." This is not consistent with language in USDA's final rule on §2.31, which states, "If the [IACUC] determines that the written narrative prepared by the principal investigator provides adequate assurance that alternatives were considered, the Committee's meeting minutes need only reflect this determination."

Keyword/literature searches are not required by either the AWA or AWR, and such searches have been shown to be ineffective[3]. The policy requirement to perform unproductive literature searches represents unnecessary regulatory burden.

Therefore, FASEB recommends that the language in USDA Animal Care Policy #12 with respect to literature searches be consistent with AWR §2.31(d)(1)(ii), which charges the IACUC

[3] Lab Anim (NY). 2012 Jul 20;41(8):230-5

to determine "that the principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals, and has provided a written narrative description of the methods and sources…". NIH's guidance should agree with USDA's.

4. Provide a minimum 60-day comment period for new OLAW policy guidance.

Agency requirements, including interpretive notes, policies, procedures manuals, terms of awards, FAQs, webinars, and journal articles, constitute a significant driver of administrative burden. These kinds of materials have proliferated over the past decade and have become *de facto* regulations. In most cases there is no input from the research community or adequate analyses of outcomes such as costs, actual impact on animal welfare, and scientific implications.

Instead of the minimum 60-day comment period proposed for new OLAW policy, FASEB recommends a 90-day comment period. As a Federation representing 30 scientific societies, we take policy development seriously. A 90-day comment period enables a more thorough and thoughtful discussion with our member societies. Any final policy, guidance, and/or FAQ should include material changes that reflect germane comments received from the stakeholder community.

Moreover, other types of guidance including (but not limited to) webinars and their transcripts, journal articles, procedure manuals, and interpretive notes should state clearly that they do not carry legal or regulatory force. Institutions are risk averse and fear being out of compliance, and this statement would reduce self-imposed burden. An example of language OLAW and USDA could utilize is: "*Agency's Name (e.g., NIH)* guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, the guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited," as suggested by the National Association for Biomedical Research.

Finally, the 21st Century Cures Act mandates that NIH, USDA, and FDA review applicable regulations and policies for the care and use of laboratory animals and to make revisions to reduce administrative burden. Given that, FASEB would encourage OLAW and USDA to open up existing guidance to a public comment period in an effort to identify additional places for burden reduction. One beneficial place to start is with the policies and guidance related to use of

non-pharmaceutical grade substances, which remain a huge source of burden for investigators and IACUCs.

5. Other approaches not previously mentioned.

a. NIH should eliminate the requirement for verification of protocol and grant congruency in NIH Grants Policy 4.1.1.2 to allow for reasonable advances, discoveries, and other developments in the overall research objectives.

The language in NIH Grants Policy 4.1.1.2 states that "It is an institutional responsibility to ensure that the research described in the application is congruent with any corresponding protocols approved by the IACUC." While differences appear to rarely occur, the requirement places emphasis on the comparison of two documents written at different times, potentially up to nine months. In addition, through amendments of and modifications to protocols over the lifetime of a study, all work conducted under PHS-funded mechanisms is covered by an approved protocol.

This disconnect has been recognized in the revised Common Rule for human subjects research, which eliminates the requirement that grant applications undergo IRB review and approval for the purposes of certification. The Common Rule agencies understood that the grant application is often outdated by the time the research study is submitted for IRB review and contains information that goes beyond the mission of the IRB to protect human subjects. NIH should follow suit and eliminate the requirement for verification of protocol and grant congruency.

There is inconsistency in these requirements. If NIH continues to insist that organizations compare the grant and animal use protocols to ensure congruency, we would encourage NIH to explain to the community what the purpose of such a comparison is – especially when differences between the two documents are rarely identified.

b. OLAW should revise FAQ C7 and PHS Policy IV.B.3.c to ensure that IACUC approved alternative strategies from "should" statements in the *Guide for the Care and Use of Laboratory Animals (Guide)* are not deemed departures or deviations and are not required to be included in the semiannual report to the Institutional Official.

The *Guide* is not a regulatory document. It is written by an independent, non-governmental organization with the stated purpose of assisting institutions in "caring for and using animals in ways judged to be scientifically, technically, and humanely appropriate." OLAW should use the

Guide as it was intended, namely, "to assist institutions in caring for and using laboratory animals in ways judged to be professionally and humanely appropriate."

The *Guide* allows facilities to produce welfare outcomes for animals in diverse and innovative ways by permitting alternative strategies to "should" statements upon approval by the IACUC. PHS Policy requires institutions to use the *Guide* as the basis for developing and implementing an institutional animal care and use program. Compliance with more than 40 "must" statements in the *Guide* regarding animal care practices is required, as is compliance with several hundred "should" statements.

Although there is no statutory or regulatory basis to consider advisory statements mandatory, OLAW's FAQ C7 states: "Deviation from a 'should' statement with IACUC approval is a departure from the Guide and must be reported in the semiannual report to the IO [Institutional Official]." This requirement does not appear to be consistent with the *Guide* language that defines a "should" statement as "a strong recommendation for achieving a goal." *Guide* authors further recognize "that individual circumstances might justify an alternative strategy." Thus, NIH should ensure that alternative strategies to "should" statements in the *Guide* are not deemed departures or deviations. They should also not be required to be included in the semiannual report given to the IO.

c. Amend the third bullet in section 8.1.2.5 of NIH Grants Policy to read "Change from the approved use of live vertebrate animals that would result in an increased risk."

For human subjects research, prior approval for a change in scope is required for "change from the approved involvement of human subjects that would result in an increased risk." If prior approval for a change in the research scope for NIH studies was only needed when increased risk to animals would result (e.g., potential for unalleviated pain/distress), the administrative burden for both investigators and IACUCs could be reduced.

d. Revise §2.31(c)(3) of the AWR to state: "The IACUC may, at its discretion, determine the best means of conducting an evaluation of the institution's programs and facilities that includes all members wishing to participate in the process. The IACUC may invite ad hoc consultants to assist in conducting the evaluation. However, the IACUC remains responsible for the evaluation and report."

AWA §2143(b)(3) requires semiannual IACUC inspection of animal facilities but does not prescribe how this should be accomplished. AWR §2.31(c)(3) says "the IACUC may determine

the best means of conducting evaluations" but then goes on to require that "at least two Committee members" participate. HREA §495(b)(3)(A) also requires a "review…in all animal study areas and facilities" but does not prescribe how that is accomplished.

Consistent with the HREA requirement, section IV.B.1-3 of the PHS Policy charges the IACUC with this review, but allows flexibility in who conducts it. Experienced reviewers who are not committee members could lend greater focus and efficiency to the process and, if managed well, free up IACUC members to focus on other aspects of IACUC activity. This would not diminish the expectation for the IACUC members to review and approve the report and address or correct any findings.

e. USDA should consider including AAALAC International accreditation as a factor in their risk assessment. This recommendation is consistent with FASEB's response to a request for comment on USDA's proposal to use third parties when determining inspection frequencies under the Animal Welfare Act[4].

The majority of citations issued to research facilities involve administrative issues and not issues involving animal care. A comparison of the FY 2007 inspection results with those for FY 2017 show the number of citations with research facility-specific issues has declined by 82 percent. A review of FY 2017 citations also finds that 2 percent of facilities accounted for 24 percent of total citations, suggesting that a risk-based inspection process incorporating compliance history would significantly improve inspection process efficiency and overall compliance with the AWR.

f. Revise the NIH guidance in NOT-OD-05-034 regarding prompt reporting to include only those incidents that jeopardized the health or well-being of animals.

In 2005, NIH released guidance (NOT-OD-05-034) outlining when noncompliance must be promptly reported[5]. In this guidance, dual purposes are identified for prompt reporting: 1) to ensure that issues affecting animal welfare are addressed and corrected, which is consistent with the language cited above, and 2) to monitor institutions' animal care and use program oversight under the PHS Policy, evaluating allegations of noncompliance, and assessing effectiveness of the PHS policies and procedures. Since the issuance of this guidance, institutions have been

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4 http://www.faseb.org/Portals/2/PDFs/opa/2018/FASEB%20Comments%20on%20Use%20of%20Third%20Party%20Inspections.pdf

5 https://grants.nih.gov/grants/guide/notice-files/not-od-05-034.html

required to routinely submit noncompliance reports even where there was no negative impact on animal welfare. Examples described in the second purpose for prompt reporting should address issues that directly affect animal health and well-being.

Feedback is sought on whether the following tools and resources are or would be helpful for reducing burden on investigators:

1. Encourage the use of sections of the AAALAC International program description in applicable parts of the OLAW Animal Welfare Assurance, for institutions accredited by AAALAC International.

The assurance for human subjects is less than five pages, and parties agree to the Terms of the Federalwide Assurance; the OLAW Domestic Assurance Sample Document is 13 pages long. A 2016 survey on the IACUC-Admin listserv found that the average institutional assurance document is 24 pages long. FASEB believes that the Animal Welfare Assurance could be streamlined considerably by using a strategy similar to the Federalwide Assurance for human subjects research. The institution would provide assurance that it and its IACUCs would fully comply with the PHS Policy and the AWA where applicable.

FASEB recognizes that these changes may require an update to PHS Policy, but we encourage OLAW to take every necessary step to reduce excess burden that does not serve a purpose in advancing animal welfare.

2. Encourage the use of the FDP Compliance Unit Standard Procedures as a repository of best practices for standard procedures used for research with animals.

The use of standard procedures for protocol development is a recommendation that members of FASEB societies highlighted in a survey responding to the National Science Board's Request for Information on administrative burden[6]. Thus, FASEB agrees that the use of the FDP Compliance Unit Standard Procedures (CUSP) could greatly reduce burden for PIs developing animal use protocols. However, we are concerned that the program is in its infancy. It has only recently started pilot testing with member organizations of the Federal Demonstration Partnership. We

[6] http://www.faseb.org/Portals/2/PDFs/opa/2014/6.7.13%20FASEB%20NSB%20Survey%20findings.pdf

caution against NIH promoting or endorsing the CUSP procedures until pilot testing is completed and any potential problems are addressed.

3. Encourage the use of the IACUC Administrators Association repository of best practices by IACUCs.

Most best practices on the IACUC Administrators Association website are behind a members only paywall. It's unclear why NIH would expect institutions to pay dues to a private organization to help reduce burden, which Congress instructed the agencies to do. While the best practices are likely helpful, FASEB doesn't believe that use of these resources would be possible for the majority of the animal use community. Encouragement of their use would not have any appreciable effect on reducing regulatory burden.

4. Encourage the use of new or existing tools to streamline protocol review through use of designated member review (DMR), DMR subsequent to full committee review, and/or Veterinary Verification and Consultation.

FASEB agrees with encouraging the use of DMR. This was another one of the recommendations that our member societies indicated in the FASEB NSB survey. Going further, however, we would encourage NIH and USDA to incorporate a risk-based approach to protocol review where DMR would be able to proceed without concurrence by the full IACUC. Please see more complete comments in response to use of DMR in proposed action number one.

We appreciate OLAW's efforts to reduce burden by introducing the Veterinary Verification and Consultation (VVC) for significant changes in 2014. However, almost four years later, several institutions in the animal care and use community are still hesitant to use VVC due to confusion over how to apply this process. Fear of being out of compliance is a major driver for IACUCs from fully implementing these strategies.

FASEB encourages OLAW to simplify the VVC significantly and trust the professional judgement of veterinarians to determine what significant changes can and cannot be approved by them. It is impossible for IACUCs to come up with a policy for every possible situation that may arise during the course of a research project. Investigators should be able to rely on the expertise of the veterinarians employed by the university to provide humane care for research animals to

approve changes to research projects. The use of VVC should not only help reduce unnecessary burden, it should also be for the benefit of the animals' welfare.

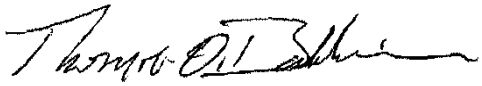
5. Expanded IACUC training activities that focus on reducing burden on investigators.

FASEB is not convinced additional training would reduce burden on investigators. As it stands now, one of the biggest drivers of administrative burden is the training component. Adding on supplementary training would seem to be counterproductive.

Having NIH and USDA state explicitly what is and is not required on all guidance/policy documents/ FAQs/etc would have the greatest impact. Institutions are risk averse and fear being out of compliance, and this statement would reduce self-imposed burden. An example of language NIH and USDA could utilize is: "*Agency's Name (e.g., NIH)* guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, the guidance describes the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited," as suggested by the National Association for Biomedical Research.

Thank you for the opportunity to respond to this Request for Information. Please feel free to contact us should you require any additional information or clarification.

Sincerely,



Thomas O. Baldwin, PhD
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