

Updates from the Office of Biotechnology Activities (OBA)

Jacqueline Corrigan-Curay, J.D., M.D.

September 12, 2013

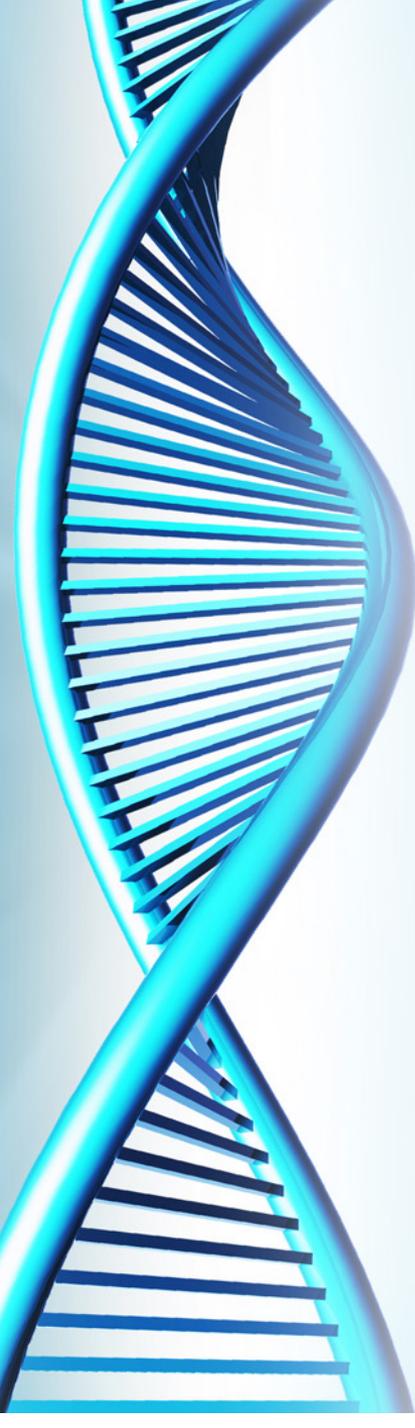




Overview

- Review public comments received on the proposal to amend the *NIH Guidelines* to allow certain multisite, low biosafety risk gene transfer trials to be exempt from Institutional Biosafety Committee (IBC) review
- Updates to Appendix B of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acids (NIH Guidelines)*--
“Classification of Human Etiologic Agents on the Basis of Hazard”

Proposed Exemption from IBC Review for Certain Multisite Trials

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Federal Register / Vol. 78, No. 92 / Monday, May 13, 2013 / Notices 27977

Agenda: To review and evaluate grant applications.
Place: Residence Inn Bethesda, 7335 Wisconsin Avenue, Bethesda, MD 20814.
Guest Person: Nancy Lewis Erwin, Ph.D., Scientific Review Officer, Scientific Review Program, Division of Extramural Activities, National Institutes of Health (NIH), 6700 Rockledge Drive, MSC 7616, Bethesda, MD 20892-7616, 301-451-7303, nancy.erwin@nih.gov.
Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)
Date: May 7, 2013.
David Clary,
Program Analyst, Office of Federal Advisory Committee Policy.
(FR Doc. 2013-11222 Filed 5-10-13; 8:45 am)
BILLING CODE: 4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Office of Biotechnology Activities; Recombinant DNA Research; Proposed Actions Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)
Office of Biotechnology Activities; Recombinant DNA Research; Proposed Actions Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)
SUMMARY: The NIH Office of Biotechnology Activities (NIH OBA) proposes to revise the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) to streamline review of certain human gene transfer trials that present a low biosafety risk. Specifically, the NIH OBA proposes to remove the requirement that Institutional Biosafety Committees (IBCs) review and approve certain human gene transfer clinical trials that use plasmids and certain attenuated, non-integrating viral vectors, provided the clinical trial follows an Initial Study in humans that was previously approved by an IBC registered with the OBA. This initial trial will have established the safety of the proposed dose of the gene transfer product (vector and transgene) in a comparable population (adults or children). The initial study should have been conducted in the same country as the proposed study to control for potential variability in infectious disease backgrounds of the participants. An initial IBC review is important to evaluate the safety of the product and to set standards for administration; however, for well-characterized vectors, in the absence of any unexpected toxicities in the initial study, subsequent biosafety assessments may not provide any additional information. While a single IBC review does not pose an undue burden, as the gene transfer field advances and more Phase II and Phase III multisite trials are developed, the time, effort and expense associated with multiple IBC reviews can be significant without adding commensurate value in the form of additional recommendations to protect the health and safety of the subject, health care worker, and community. IBCs play a critical role in the evaluation of new products and their review can inform other oversight bodies, such as Institutional Review Boards. However, given the competing demands on IBCs, this change will provide IBCs with the option of focusing their efforts on those clinical trials where review will be most productive. While IBCs will no longer be required to review all clinical trials using the same product, each institution can implement its own policies regarding the need to review such trials and the information that a principal investigator (PI) should submit regarding the safety of the previous trial. For example, an institution may designate the Biological Safety Officer and the IBC Chair to review data from the initial trial and determine whether a subsequent trial using the same agent meets the exemption criteria outlined herein. The institution may also set its own policies regarding the need for the PI to inform the IBC about enrollment, any relevant new biosafety findings, and completion of the trial. This policy will only exempt human gene transfer clinical trials from IBC review under Section III-C-1. It does not apply to basic, nonclinical research. In addition, it does not create an exemption from registration of the trial with the NIH OBA or the Recombinant DNA Advisory Committee (RDAC) review and reporting requirements. By continuing to require registration and reporting on these trials, the NIH OBA will be able to continue to monitor adverse events or incident reports of accidental exposures by health care workers delivering these agents and, if necessary, provide information regarding these events to investigators, IBCs, and the public. The NIH OBA will also be able to assess whether this change in policy has any adverse impact on the biosafety of gene transfer trials.
DATES: All comments should be submitted by June 12, 2013.
ADDRESSES: Comments may be submitted to the NIH OBA by email at oba@od.nih.gov; by fax to 301-496-9839; or by mail to the NIH Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892-7985. All written comments received in response to this notice will be available for public inspection in the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland, weekdays between the hours of 8:30 a.m. and 5:00 p.m.
FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional information about these proposed changes, please contact the NIH OBA by email at oba@od.nih.gov or telephone at 301-496-9838. Comments

Comment period closed
June 12, 2013

<http://oba.od.nih.gov/oba/rac/2013-11222-FR-Notice.pdf>



Impetus for Proposal

- **A number of gene transfer clinical trials are conducted utilizing vectors for which there is considerable clinical experience and biosafety risks are well characterized**
- **A mechanism to streamline review of low biosafety risk trials could help facilitate research, especially for multisite trials, without compromising the safety of trial conduct**



Vectors Eligible for Exemption from IBC Review (Proposed)

- Non-integrating viral vectors derived from the following RG2 or lower viruses are eligible:
 - Adenovirus, serotypes 2 or 5
 - Poxviruses, except for vaccinia
 - HSV-1
 - AAV, all serotypes*
- Viral vectors eligible for exemption must be attenuated, demonstrated in preclinical and by experience in clinical trial

* AAV vectors are not primarily designed to integrate and are more likely to remain episomal but integration does occur



Exemption From IBC Review for Multisite Trials Proposed

- In order to be eligible for an exemption from IBC review, an initial trial in the same country must be complete and the new trial seeking the exemption must use the same vector and transgene and have a comparable trial design.
- A comparable trial design includes the following elements:
 - Same delivery method (e.g., data from an intratumoral administration study cannot be used to exempt an intravenous administration study)
 - Comparable concomitant interventions as in the initial safety trial
 - Same dose as tested in phase I trial
 - Age
If the multisite trial will enroll pediatric subjects, the initial trial must have enrolled pediatric subjects at the dose to be tested

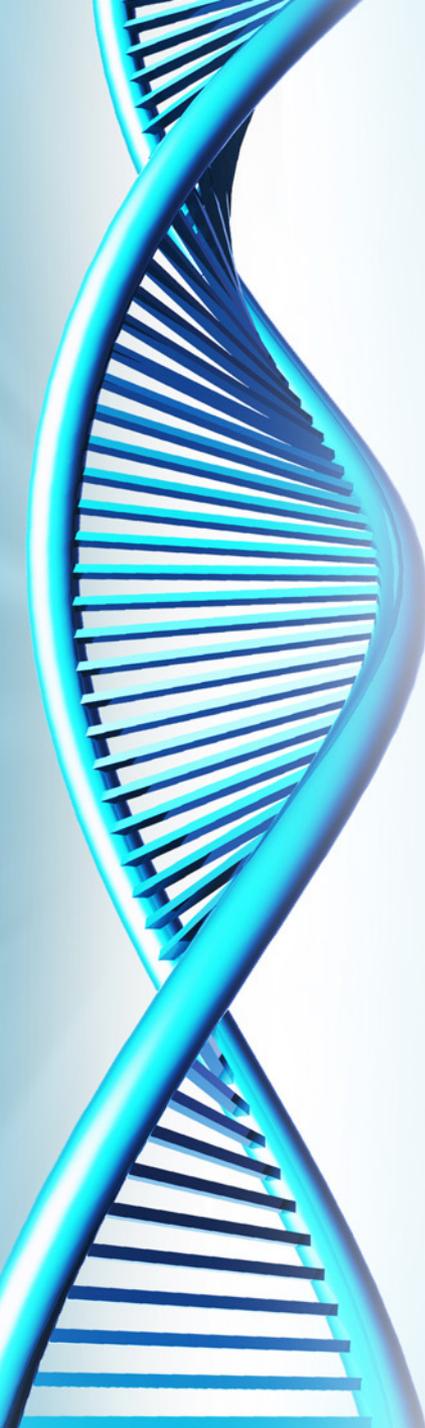


Local Level Exemption Process

- **IBCs would be given flexibility to devise implementation policies:**
 - **What would be the process for making a decision that a trial is exempt?**
 - **Would there be a registration system for exempt trials with limited reporting?**
 - **Would the IBC rely on another institution's decision that a trial is exempt?**
- **These changes would not affect whether a trial must be registered with the Office of Biotechnology Activities and undergo review by the NIH Recombinant DNA Advisory Committee**

Public Comments

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- **Institutions/Individuals**
 - **American Biological Safety Association**
 - **Biosafety Officer or IBC representative**
 - **Johns Hopkins University**
 - **Illinois State University**
 - **Fred Hutchinson Cancer Research Center**
 - **Stanford University**
 - **Representative from commercial IBCs**
 - **Investigator from the U.S. military HIV research program**
 - **Director, rare disease foundation**
 - **Global health consultant**



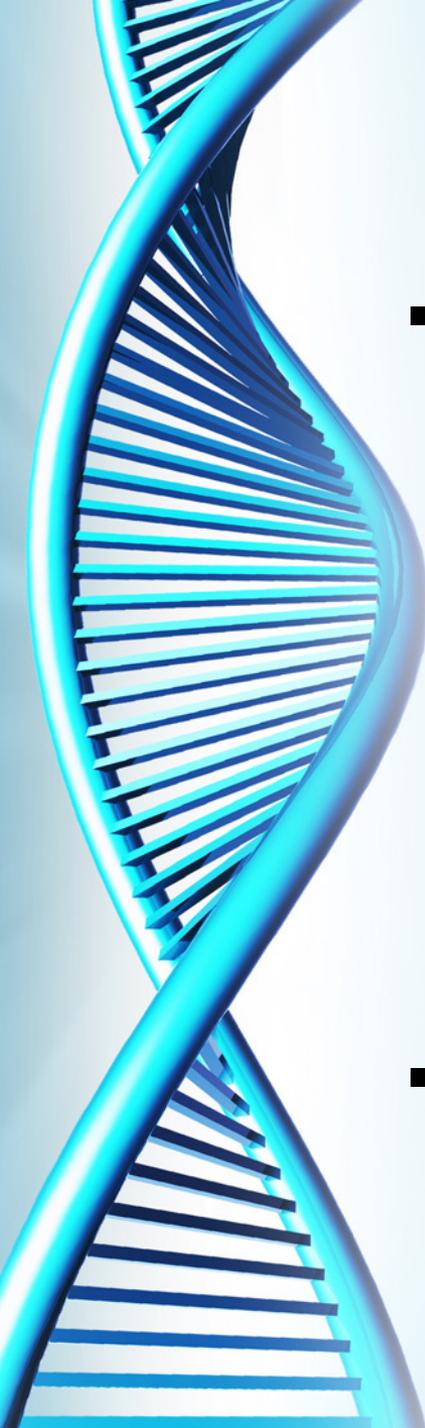
Overall Comments

- **A few comments advocate moving forward and even recommended that we consider going further and exempting all trials that are exempt under Appendix M-VI (“vaccine exemption”) from IBC review**
- **The majority of comments were supportive of the general goal to make review of multisite trials more efficient, but had significant concerns regarding this proposal**



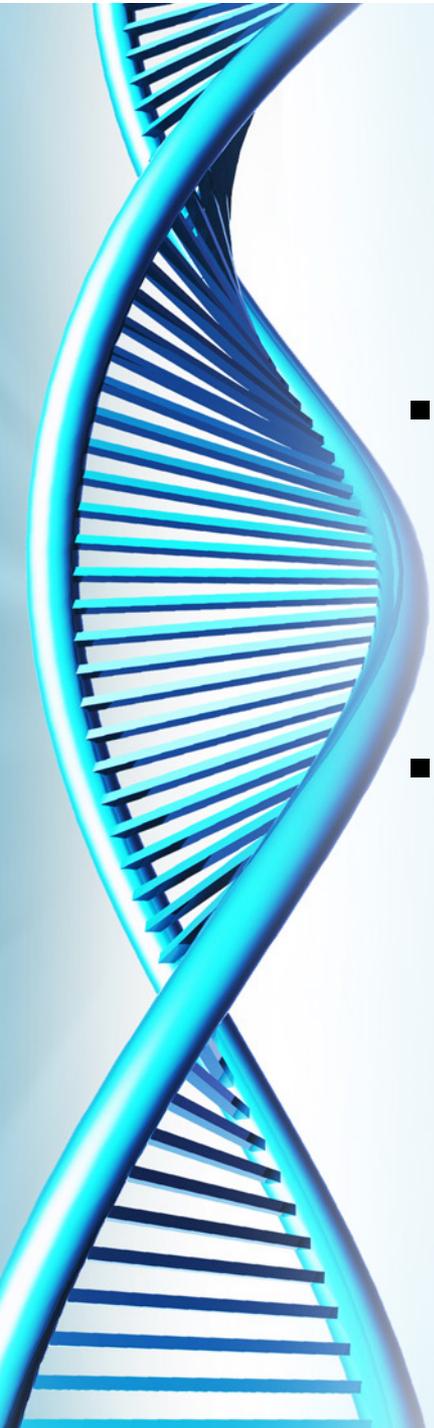
General Concerns Raised in Comments

- **Reliance on one or two initial IBC reviews assumes that the quality and depth of IBC review is uniform**
 - **If an issue is missed during the initial review, there will not be a subsequent review to address that issue**
- **The proposal fails to take into account the importance of IBC review to ensure that there are site-specific protocols in place, including, for example, blood-borne pathogen training, written exposure control plans, adequate availability of personal protective equipment and training on its use, secure storage facilities, and adequate access to handwashing sinks and eye wash units**
- **The proposal will reduce oversight and may weaken safety**



Specific Concerns – Vectors

- **Vector Choice**
 - The exemption for pox viruses should be clarified not to include monkey pox
 - The inclusion of Ad 5 and Ad 2 should be reconsidered in light of the findings in three Ad vectored vaccine trials in which increased HIV infection was observed in subjects with pre-existing immunity to adenovirus
 - The inclusion of AAV should be reconsidered because it has the ability to integrate and this may lead to serious adverse events
- **Determination of attenuation**
 - On what basis will the determination be made that the vector is attenuated and by whom?
 - Will it be made consistently?



Specific Issues Raised– Trial Design

- **What happens if the trial design changes once the trial is enrolling (e.g. change in dose, concomitant interventions, delivery)? Does enrollment need to stop and IBC review be obtained?**
- **In addition to radiation and chemotherapy interventions, there are a number of immunomodulatory agents available that should be considered when evaluating whether the trial design is comparable**
 - **Will this include other causes of immune suppression, e.g. previous treatments ?**



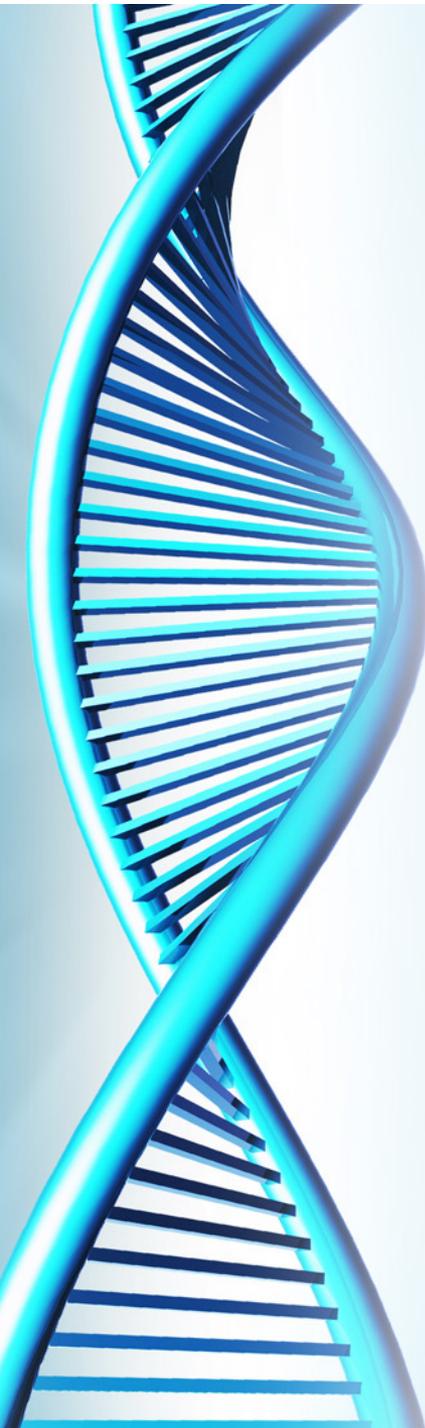
Specific Issues Raised – Implementation

- **Will the institution/IBC receive be able to review any new data regarding the safety of the construct if the trial is exempt?**
- **If an otherwise exempt trial is reviewed at some but not all sites, will that limit the amount of safety data that an IBC will see on a multisite trial?**



Next Steps

- **In light of these substantive concerns, OBA proposes to revisit this proposal with the RAC to see if there are ways to address these outstanding issues:**
 - **The potential for this exemption to reduce oversight**
 - **The ability to uniformly implement this change across IBCs**



Updates to Appendix B

- Appendix B of the *NIH Guidelines* designates the Risk Group (RG) classification of microorganisms based upon their ability to cause disease in healthy adults and our ability to treat or prevent such disease
- Although, the RG of an organism does not determine the containment level for research with that organism, generally the RG and level of containment are correlated, e.g. a RG3 agent is generally worked with at BL3
 - In certain cases, however, the experimental manipulations may warrant higher containment



Updates to Appendix B

- Based on consultation with experts from the NIAID, NIH, the CDC, and current and former members of the RAC, the following microorganisms will be added to Appendix B:
 - Middle East Respiratory Syndrome coronavirus (MERS-CoV) as a RG3 coronavirus
 - *Pseudomonas aeruginosa* as a RG2 bacteria