Failure to make required disclosures can result in any of the remedies described in 45 CFR 75.371 Remedies for noncompliance, including suspension or debarment (See 2 CFR parts 180 & 376 and 31 U.S.C. 3321).

VII. Agency Contacts

1. Questions on the programmatic issues may be directed to: Shannon Beyale, Health Information Specialist, Office of Urban Indian Health Programs, 5600 Fishers Lane, Mail Stop: 08E65D, Rockville, MD 20857, Phone: (301) 945–3657, Fax: (301) 443–8446, Email: *Shannon.Beyale@ihs.gov*.

2. Questions on grants management and fiscal matters may be directed to: Donald Gooding, Grants Management Specialist, 5600 Fishers Lane, Mail Stop: 09E70, Rockville, MD 20857, Phone: (301) 443–2298, Fax: (301) 594–0899, Email: *Donald.Gooding@ihs.gov*.

3. Questions on systems matters may be directed to: Paul Gettys, Grant Systems Coordinator, 5600 Fishers Lane, Mail Stop: 09E70, Rockville, MD 20857, Phone: (301) 443–2114; or the DGM main line (301) 443–5204, Fax: (301) 594–0899, Email: *Paul.Gettys@ihs.gov*.

VIII. Other Information

The Public Health Service strongly encourages all grant, cooperative agreement and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103–227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of the facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the HHS mission to protect and advance the physical and mental health of the American people.

Michael D. Weahkee,

RADM, Assistant Surgeon General, U.S. Public Health Service, Principal Deputy Director, Indian Health Service.

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BILLING CODE 4165–16–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Final Action Under the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

AGENCY: National Institutes of Health, HHS.

ACTION: Notice of changes to the *NIH Guidelines*.

SUMMARY: This notice sets forth final changes to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*) to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements already captured within the existing regulatory framework, as initially outlined by the NIH Office of Science Policy (OSP) in a **Federal Register** notice issued on August 17, 2018. Following the solicitation of public comment on its original proposal, the NIH is amending the *NIH Guidelines* to: (A) Delete the NIH protocol registration submission and reporting requirements under Appendix M of the *NIH Guidelines,* and (B) modify the roles and responsibilities of entities that involve human gene transfer and the Recombinant DNA Advisory Committee (RAC).

DATES: Changes outlined in this notice will be effective upon publication in the **Federal Register**.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional background information about these changes, please contact the NIH by email at *SciencePolicy@od.nih.gov,* or telephone at 301–496–9838. You may also contact Jessica Tucker, Ph.D., Director of the Division of Biosafety, Biosecurity, and Emerging Biotechnology Policy, Office of Science Policy, NIH, at 301–451–4431 or *Jessica.Tucker@nih.gov.*

SUPPLEMENTARY INFORMATION: In a **Federal Register** notice issued on August 17, 2018 (83 FR 41082), the NIH proposed a series of actions to the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)* to streamline oversight of human gene transfer research (HGT), and to focus the *NIH Guidelines* more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The field of HGT has recently experienced a series of advances that has resulted in the translation of research into clinical practice, including Food and Drug Administration (FDA) approvals for licensed products. Additionally, oversight mechanisms for ensuring HGT is appropriately assessed for safety risks have sufficiently evolved to keep pace with new discoveries in this field. At this time, there is duplication in submitting protocols, annual reports, amendments, and serious adverse events for HGT protocols to both the NIH and the FDA that does not exist for other areas of clinical research. It is an opportune time to make changes to the *NIH Guidelines* to make oversight of HGT commensurate with oversight afforded to other areas of clinical research, given the robust infrastructure in place to oversee this type of research.

After careful consideration of public comments, the NIH is amending the *NIH Guidelines* in the following areas:

1. Elimination of HGT protocol submission and reporting requirements to the NIH, and individual HGT protocol review by the Recombinant DNA Advisory Committee (RAC).

2. Modification of roles and responsibilities of investigators, institutions, Institutional Biosafety Committees (IBCs), the RAC, and the NIH to be consistent with these goals including:

a. Modification of roles of IBCs in reviewing HGT to be consistent with review of other covered research.

b. Elimination of roles of the RAC in HGT and biosafety.

The proposed changes outlined above will require amendment of multiple portions of the *NIH Guidelines* (see section below on ''Amendments to the *NIH Guidelines*''). Following deletions, sections and appendices will be relabeled to proceed consecutively throughout the *NIH Guidelines.* Language in the ''Amendments to the *NIH Guidelines*'' section below includes updated references to relabeled section and appendix names, where relevant. Sections of the *NIH Guidelines* also will be amended to include several minor additional changes to provide non-substantive clarifications or for consistency.

Overview of Comments Received in Response to NIH's Proposal To Amend the *NIH Guidelines* (83 FR 41082)

The NIH received 43 comments (available at *https://osp.od.nih.gov/wp-content/uploads/Aug162018_AllComments_r508.pdf*) in response to its proposal to amend the *NIH Guidelines,* posted in the **Federal Register** on August 17, 2018, including from individuals from the general public, academic institutions, and industry; and professional or membership organizations representing the biosafety, gene therapy, biotechnology, patient advocacy, academic, medical, and Institutional Review Board (IRB) communities. Few comments received in response to the **Federal Register** notice (83 FR 41082) (hereafter referred to as the August 17, 2018 FRN) reflected views entirely supportive of or in opposition to the proposal, but instead indicated support

or criticism for specific components. A minority of comments indicated that the existing system for review and reporting of individual protocols and IBC review should remain, as is. All comments, regardless of position, were reviewed and considered by the NIH. These comments, along with the NIH responses, are summarized below.

Elimination of submission and reporting requirements to the NIH. In general, the majority of favorable comments supported eliminating HGT protocol submission and safety reporting requirements to the NIH's Office of Science Policy (NIH/OSP) and streamlining HGT oversight to eliminate overlapping reporting requirements, though a smaller number of comments did not support this proposed change. Some respondents indicated that reporting of HGT protocols to both the FDA, which has regulatory jurisdiction, and the NIH is no longer necessary. After careful analyses of these comments, the NIH will implement the changes to protocol submission and reporting requirements as outlined in the August 17, 2018 FRN. Related to this issue, some comments indicated an interest in maintaining the Genetic Modification Clinical Research Information System (GeMCRIS) or ensuring vector information gets added to *ClinicalTrials.gov* to provide IBCs with a resource for use during their reviews. Of note, the operation of GeMCRIS and its maintenance are not specified in the *NIH Guidelines;* because NIH/OSP will no longer receive HGT protocols and associated reports, GeMCRIS will no longer be updated. The NIH will continue to consider appropriate mechanisms to facilitate information-sharing, and *ClinicalTrials.gov* provides some useful data for those in the HGT community. The NIH notes that the level of detailed information that is currently housed in GeMCRIS is not standard for other clinical research, or other non-clinical research subject to the *NIH Guidelines.*

IBC Roles and Responsibilities. Most comments received from individuals self-identifying as members of the biosafety community were supportive of continued review and oversight of HGT by IBCs. However, many comments noted concerns about the appropriate roles and responsibilities for IBCs, especially in the area of HGT oversight, in light of these proposed changes. In general, the NIH agrees that further consideration of the roles and responsibilities of IBCs in the assessment of biosafety issues associated with HGT is warranted, and the NIH anticipates exploring these issues with the community in more detail. However, the NIH notes that biosafety oversight of HGT protocols has always been the responsibility of IBCs, and they should continue to serve that function. Local oversight is an important component of the *NIH Guidelines,* and IBCs are expected to continue to have the necessary expertise and processes in place to consider biosafety issues associated with HGT protocols, as they do for other research covered under the *NIH Guidelines.* Upon assessment of the comments, the NIH will implement the changes outlined in the August 17, 2018 FRN regarding IBC roles and responsibilities with two exceptions noted below. Specific sub-topics raised in comments received included the duration of IBC oversight, IBC responsibilities and documents to review, and the scope of biosafety review for HGT protocols.

Several comments requested additional clarity from the NIH regarding the expected duration of IBC oversight and whether this oversight should extend beyond the proposed final administration of product. Specifically, some comments questioned whether oversight should be extended until it is reasonable to expect that the vector will no longer be shed, until there is no product at the site of the study, until the trial is no longer enrolling, or throughout handling of biospecimens taken from individuals after the final dose. The NIH acknowledges these issues and notes that biosafety issues that extend beyond product administration should be considered by IBCs during review, but any such risks should generally be addressed and managed by IBCs prior to administration (*e.g.,* establishing monitoring plans for shedding). Additionally, the *NIH Guidelines* set a baseline for IBC oversight requirements, and institutions regularly choose to expand this scope based upon research oversight needs; for example, many IBCs extend oversight to all pathogen research, regardless of whether this research is recombinant or synthetic in origin. As such, institutions and IBCs may always choose to expand the purview of their oversight as needed to maintain appropriate oversight over biosafety issues. The *NIH Guidelines* will be amended in Section IV–B–2–b–(1) to clarify that oversight may conclude after the final administration of product to the final research participant, but institutions and IBCs are permitted to identify an end point for the conclusion of oversight that extends after the final administration of the product to the final research participant.

Many comments requested additional guidance on what documents IBCs should review regarding HGT protocols; a majority of these comments were received from individuals self-identifying as associated with research institutions or biosafety professionals. Specific recommendations included retaining Appendix M–1–A in the *NIH Guidelines* or, as a resource, providing a checklist of documents or developing another guidance document. The *NIH Guidelines,* in general, are intended to provide sufficient clarity, but also sufficient flexibility, to all institutions to establish policies that accommodate local needs while adhering to the principles and expectations detailed in the policy. For both basic research and HGT, institutions should establish policies to ensure that documentation is sufficient for oversight bodies, including IBCs, to conduct review and approval. Because NIH/OSP sometimes issues guidance or points to consider on specific topics relevant to the *NIH Guidelines* when requested by the community, NIH/OSP will make available the parts of Appendix M–1–A that are still relevant, in light of the final changes to the *NIH Guidelines,* as a separate resource for institutions, IBCs, and investigators on the types of information that institutions and IBCs may wish to consider in the review of HGT protocols.

Similarly, many comments requested more guidance on what IBCs should consider when reviewing HGT protocols for biosafety considerations. A small number of respondents suggested that the biosafety review of HGT protocols is no longer needed, is very low risk, or reflects substantial burden without a commensurate benefit. Others indicated that reporting of adverse events to IBCs and IBC review of informed consent documents should be required to enable IBCs to conduct sufficient biosafety reviews. A few comments indicated the proposed changes will more clearly delineate the roles of IBCs and IRBs and supported the notion that review of informed consent documents or adverse events should not be a responsibility of IBCs but is instead the purview of IRBs. Others expressed confusion about whether reporting biosafety incidents to NIH/OSP would be affected by the proposed amendments to the *NIH Guidelines.* The proposed changes ensure that the scope and responsibilities of IBCs reviewing HGT protocols are consistent with their responsibilities for other research covered by the *NIH Guidelines.* As noted previously, institutions may expand the scope of IBC review of

protocols and safety reports beyond that outlined by the *NIH Guidelines,* but in general, review of adverse events and informed consent documents is the purview of other oversight entities. The topics for IBC biosafety review for HGT protocols are articulated in Section IV–B–2–b–(1). No changes were proposed regarding the reporting of biosafety incidents to NIH/OSP for HGT protocols, and this reporting will continue to be required under the *NIH Guidelines* as articulated in Sections IV–B–1–j, IV–B–2–b–(7), and IV–B–7–a–(3).

Some comments indicated that the proposal to eliminate certain protocols conducted under individual patient expanded access investigational new drug applications (INDs) as research subject to the *NIH Guidelines* is not justifiable from a biosafety perspective, since the biohazard risks are not different from those under a conventional human gene therapy IND. This change was proposed to harmonize the *NIH Guidelines* with current FDA policies, which do not require review by the full IRB membership of physician-sponsored individual patient expanded access INDs. Some modifications to the original proposed language will be made to ensure greater consistency with existing FDA guidance. Specific guidance regarding FDA requirements is provided at *https://www.fda.gov/downloads/drugs/guidances/ucm351261.pdf.* Section III–C–1 will be amended to clearly state that any deliberate transfer of recombinant or synthetic nucleic acids into one human participant, when conducted under an FDA-regulated individual patient expanded access IND or protocol, including for emergency use, is not research subject to the *NIH Guidelines.*

Elimination of RAC's Roles in HGT Protocol Review and Biosafety Oversight from the NIH Guidelines, and Future of the RAC. A topic that generated many comments concerned the proposed changes to the role of the RAC as specified in the *NIH Guidelines.* Some comments indicated support for eliminating RAC review of individual HGT protocols and focusing the committee's attention on a broader scope of emerging biotechnologies, whether or not such research involves recombinant or synthetic nucleic acid molecules, because IBCs can adequately perform their HGT oversight independently and the FDA has regulatory authority. Upon assessment of the comments, the NIH will implement the changes outlined in the August 17, 2018 FRN regarding RAC roles with two additions noted below. Specific sub-topics raised in comments received included removal of references to the role of the RAC from the *NIH Guidelines,* the need for a transparent forum for discussion on various scientific, ethical, legal and social issues related to emerging biotechnologies, the loss of the RAC as a biosafety guidance resource for IBCs, potential future roles of the RAC, and which entities should perform current roles of the RAC.

Some respondents indicated that the biosafety roles of the RAC in the *NIH Guidelines* should remain, with some suggesting that the articulation of RAC functions in the *NIH Guidelines* protects the committee's core functions more than a committee charter. The NIH notes that, in general, functions of discretionary Federal Advisory Committee Act (FACA) committees, such as the RAC, are routinely articulated in their charters rather than in policy documents. The NIH is committed to transitioning the RAC in ways that preserve its current forum for public discourse and advice to the NIH Director on the emerging biotechnology issues of today and the future. The NIH will release the revised charter of the committee, which will be renamed the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC), to reflect the shift in focus of the committee while embracing the continuity of this important advisory board. Some historical references to the RAC will remain in the *NIH Guidelines.*

Some comments, particularly those from individuals self-identifying as members of the ethics and oversight communities, indicated the importance of a transparent forum for discourse and advice regarding HGT, Major Actions, biosafety issues, and any changes needed to the *NIH Guidelines.* Some respondents argued that there are still unknown aspects of HGT, especially given the advent of genome editing technologies, and that the existing system of oversight and other relevant mechanisms (*i.e.,* the FDA, IRBs, and *ClinicalTrials.gov*) do not replace the RAC's functions and mission of transparency. Additionally, one commenter suggested that although few individual protocols have been publicly reviewed since the 2016 amendments to the *NIH Guidelines,* the RAC members may have chosen to review more protocols had they been given the opportunity. While no longer specified as responsibilities in the *NIH Guidelines,* the NIH will continue to consult, as needed, with the NExTRAC or other relevant advisory committees regarding issues of emerging biotechnologies, biosafety, or when proposing changes to the *NIH Guidelines* or other relevant policies. The NIH consistently seeks out diverse input, including expert opinions, when considering changes to existing policies, and transparent and open discourse is a critical part of the policy-making process, whether through requests for public comment, workshops, or charges to advisory committees. Integral to the NIH mission is to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science, and the NIH has and will continue to rely on mechanisms that allow for advice and public discourse, including review and discussion by FACA committees, when appropriate.

Several comments indicated that the public discussion of HGT protocols by the RAC provided guidance to IBCs in conducting biosafety reviews of these protocols. A few comments indicated that IBCs do not have the necessary expertise to conduct biosafety reviews for clinical protocols and therefore rely on the RAC. Some commenters requested that IBCs should retain flexibility to request RAC review for certain individual HGT protocols, especially those involving pediatric populations. Alternatively, other respondents suggested that the NIH should establish a panel of HGT experts to provide guidance, upon request. While the NIH is sensitive to these concerns and acknowledges that risks are always present in clinical research, the NIH argues that there is not sufficient evidence to justify the unique oversight afforded to this area of research. The NIH maintains, however, that the NExTRAC will continue to serve as a forum for public discourse and discussions on emerging biotechnology issues, which may include—but is not limited to—emerging trends in HGT, rather than the discussion of individual HGT protocols. Furthermore, the NIH emphasizes that all HGT protocols, regardless of whether RAC review was performed, were and are to be reviewed by IBCs. To assert that this function cannot be performed in the absence of RAC review undermines the authority of the IBC and the underlying rationale for establishing the oversight infrastructure. IBCs are expected to include and, as needed, supplement their discussions with *ad hoc* expertise for the local biosafety review of all protocols under their purview, including HGT protocols. For Major Actions and other biosafety issues of significance, the NIH will continue to, as needed, consult with subject matter experts and, if necessary, provide a forum for public discussion to facilitate the review and approval process.

Several comments suggested support for the NIH's intent to continue to utilize the RAC as an emerging biotechnology committee but requested more information about these plans. Similarly, some comments requested that the NIH identify a point of contact to assist in navigating questions that previously would have been considered by the RAC. Regarding the future of the RAC, as noted, the NIH will issue a revised charter and intends to use the NExTRAC as a board for public discussion and advice on the scientific, safety, ethical, legal, and social issues associated with emerging biotechnologies. NIH/OSP continues to serve as a resource for guidance, which it provides to investigators, institutions, biosafety professionals, and members of the public on a daily basis. Questions regarding the *NIH Guidelines* should continue to be directed to *NIHGuidelines@od.nih.gov.*

Two references to the RAC that also should have been proposed for elimination from the *NIH Guidelines* were not included in amendments proposed in the August 17, 2018 FRN. These references will be included for elimination in the final changes; otherwise, all changes outlined in the August 17, 2018 FRN regarding the RAC will be implemented.

Other Topics Outside of this Policy Proposal. Some comments requested additional guidance in the *NIH Guidelines* on specific areas of emerging technology, including CRISPR/Cas9 genome editing and T cell immunotherapy, perhaps by utilizing a task force to provide such guidance. Additionally, a few comments requested further assessment of mature areas of technology to determine if they should still be subject to the *NIH Guidelines.* A small number of comments requested further guidance regarding *in utero* gene therapy. These types of amendments were not the purview of this policy change, but the NIH is undertaking a long-term effort to consider further updates to the *NIH Guidelines,* building upon the July 2017 workshop, *NIH Guidelines:* Honoring the Past, Charting the Future. The NIH will continue to solicit input and facilitate transparent discourse to consider these and similar issues.

Other comments outside the purview of this proposed policy change, but which may be addressed in future efforts, were related to requested modifications of the IBC review and approval process, including allowing expedited review, eliminating the requirement for IBC review at sites lacking IBCs, and greater guidance for coordination between various oversight committees (*e.g.,* IBCs, IRBs, and Institutional Animal Care and Use Committees) or coordination on multisite trials. As noted previously, the NIH is committed to considering the appropriate roles of IBCs in biosafety review of clinical research and will continue to consider these issues.

Amendments to the NIH Guidelines

Section I–A will be amended as follows:

Section I–A. Purpose

The purpose of the *NIH Guidelines* is to specify the biosafety practices and containment principles for constructing and handling: (i) Recombinant nucleic acid molecules, (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and (iii) cells, organisms, and viruses containing such molecules.

Section I–A–1 will be amended as follows:

Section I–A–1. Any nucleic acid molecule experiment, which according to the *NIH Guidelines* requires approval by NIH, must be submitted to NIH or to another Federal agency that has jurisdiction for review and approval. Once approvals, or other applicable clearances, have been obtained from a Federal agency other than NIH (whether the experiment is referred to that agency by NIH or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval.

Section I–A–1–a will be amended as follows:

Section I–A–1–a. For experiments involving the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research participants (human gene transfer), no human gene transfer experiment shall be initiated (see definition of initiation in Section I–E–4) until Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained and all other applicable institutional and regulatory authorization(s) and approvals have been obtained.

Section I–E. General Definitions will be amended to delete the current definitions I–E–4, and I–E–7 through I–E–12 and to include a new definition for ''*initiation.*''

Section I–E–4 will be amended to define initiation as follows: ''Initiation'' of research is the introduction of recombinant or synthetic nucleic acid molecules into organisms, cells, or viruses.

None of the other sub-sections under Section I. Scope of the NIH Guidelines will be amended.

Section III will be amended as follows:

Section III. Experiments Covered by the *NIH Guidelines*

This section describes six categories of experiments involving recombinant or synthetic nucleic acid molecules: (i) Those that require NIH Director approval and Institutional Biosafety Committee (IBC) approval before initiation (see Section III–A), (ii) those that require NIH OSP approval and Institutional Biosafety Committee approval before initiation (see Section III–B), (iii) those that require Institutional Biosafety Committee approval before initiation of human gene transfer (see Section III–C), (iv) those that require Institutional Biosafety Committee approval before initiation (see Section III–D), (v) those that require Institutional Biosafety Committee notification simultaneous with initiation (see Section III–E), and (vi) those that are exempt from the *NIH Guidelines* (see Section III–F).

Note: *If an experiment falls into Sections III–A, III–B, or III–C and one of the other sections, the rules pertaining to Sections III–A, III–B, or III–C shall be followed.* If an experiment falls into Section III–F and into either Sections III–D or III–E as well, the experiment is considered exempt from the *NIH Guidelines.*

Any change in containment level, which is different from that which is specified in the *NIH Guidelines,* may not be initiated without the express approval of NIH OSP (see Section IV–C–1–b–(2) and its subsections, *Minor Actions*).

Section III–A will be amended as follows:

Section III–A. Experiments That Require NIH Director Approval and Institutional Biosafety Committee Approval Before Initiation (See Section IV–C–1–b–(1), Major Actions)

Section III–A–1. Major Actions Under the *NIH Guidelines*

Experiments considered as *Major Actions* as defined in Section III–A–1–a under the *NIH Guidelines* cannot be initiated without submission of relevant information on the proposed experiment to the Office of Science Policy, National Institutes of Health, preferably by email to: *NIHGuidelines@od.nih.gov,* the publication of the proposal in the **Federal Register** for a minimum of 15 days of comment, and notice of specific approval by NIH. The containment

conditions or stipulation requirements for such experiments will be set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D, *Major Actions Taken under the NIH Guidelines.*

Section III–A–1–a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V–B, *Footnotes and References of Sections I–IV*), if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will require NIH Director approval.

Consideration should be given as to whether the drug resistance trait to be used in the experiment would render that microorganism resistant to the primary drug available to and/or indicated for certain populations, for example children or pregnant women.

At the request of an Institutional Biosafety Committee, NIH OSP will make a determination regarding whether a specific experiment involving the deliberate transfer of a drug resistance trait falls under Section III–A–1–a and therefore requires NIH Director approval. An Institutional Biosafety Committee may also consult with NIH OSP regarding experiments that do not meet the requirements of Section III–A–1–a but nonetheless raise important public health issues.

Section III–C will be amended as follows:

Section III–C. Experiments Involving Human Gene Transfer That Require Institutional Biosafety Committee Approval Prior to Initiation

Section III–C–1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived From Recombinant or Synthetic Nucleic Acid Molecules, Into One or More Human Research Participants

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or

2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules that meet any one of the following criteria:

a. Contain more than 100 nucleotides; or

b. Possess biological properties that enable integration into the genome (*e.g., cis* elements involved in integration); or

c. Have the potential to replicate in a cell; or

d. Can be translated or transcribed.

Research cannot be initiated until Institutional Biosafety Committee and all other applicable institutional and regulatory authorization(s) and approvals have been obtained.

The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under an FDA-regulated individual patient expanded access IND or protocol, including for emergency use, is not research subject to the *NIH Guidelines* and thus does not need to be submitted to an IBC for review and approval.

Section III–D–7–b will be amended as follows:

Section III–D–7–b. Highly Pathogenic Avian Influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1). Experiments involving influenza viruses containing a majority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced containment, (see Appendix G–II–C–5, *Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses*). Experiments involving influenza viruses containing a minority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced unless a risk assessment performed by the IBC determines that they can be conducted safely at BL2 and after they have been excluded pursuant to 9 CFR 121.3(e). NIH OSP is available to IBCs to provide consultation with influenza virus experts when risk assessments are being made to determine the appropriate biocontainment for experiments with influenza viruses containing a minority of gene/segments from HPAI H5N1. Such experiments may be performed at BL3 enhanced containment or containment may be lowered to BL2, the level of containment for most research with other influenza viruses. (USDA/APHIS regulations and decisions on lowering containment also apply.) In deciding to lower containment, the IBC should consider whether, in at least two animal models (*e.g.,* ferret, mouse, Syrian golden hamster, cotton rat, non-human primate), there is evidence that the resulting influenza virus shows reduced replication and virulence compared to the parental RG3 virus at relevant doses. This should be determined by measuring biological indices appropriate for the specific animal model (*e.g.,* severe weight loss, elevated temperature, mortality or neurological symptoms).

Section III–D–7–d will be amended as follows:

Section III–D–7–d. Antiviral Susceptibility and Containment. The availability of antiviral drugs as preventive and therapeutic measures is an important safeguard for experiments with 1918 H1N1, HPAI H5N1, and human H2N2 (1957–1968). If an influenza virus containing genes from one of these viruses is resistant to both classes of current antiviral agents, adamantanes and neuraminidase inhibitors, higher containment may be required based on the risk assessment considering transmissibility to humans, virulence, pandemic potential, alternative antiviral agents if available, etc.

Experiments with 1918 H1N1, human H2N2 (1957–1968) or HPAI H5N1 that are designed to create resistance to neuraminidase inhibitors or other effective antiviral agents (including investigational antiviral agents being developed for influenza) would be subject to Section III–A–1 (*Major Actions*). As per Section I–A–1 of the *NIH Guidelines,* if the agent is a Select Agent, the NIH will defer to the appropriate Federal agency (HHS or USDA Select Agent Divisions) on such experiments.

Section III–F–6 will be amended as follows:

Section III–F–6. Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the NIH Director after appropriate notice and opportunity for public comment (see Section IV–C–1–b–(1)–(c), *Major Actions*). See Appendices A–I through A–VI, *Exemptions under Section III–F–6—Sublists of Natural Exchangers,* for a list of natural exchangers that are exempt from the *NIH Guidelines.*

Section III–F–8 will be amended as follows:

Section III–F–8. Those that do not present a significant risk to health or the environment (see Section IV–C–1–b–(1)–(c), *Major Actions*), as determined by the NIH Director following appropriate notice and opportunity for public comment. See Appendix C, *Exemptions under Section III–F–8* for other classes of experiments which are exempt from the *NIH Guidelines.*

None of the other sub-sections under Section III. Experiments Covered by the NIH Guidelines will be amended.

Section IV–B–1–f will be amended as follows:

Section IV–B–1–f. Ensure that when the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human participants: (i) The Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary), and (ii) no human gene transfer experiment shall be initiated until Institutional Biosafety Committee approval has been obtained, and all other applicable institutional and regulatory authorization(s) and approvals have been obtained. Institutional Biosafety Committee approval must be obtained from the clinical trial site.

Section IV–B–2–a–(1) will be amended as follows:

Section IV–B–2–a–(1). The Institutional Biosafety Committee must comprise no fewer than five members so selected that they collectively have experience and expertise in recombinant or synthetic nucleic acid molecule technology and the capability to assess the safety of recombinant or synthetic nucleic acid molecule research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (*e.g.,* officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when experiments utilizing Appendix L, *Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Plants,* require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix M, *Physical and Biological Containment for Recombinant or Synthetic Nucleic Acid Molecule Research Involving Animals,* require Institutional Biosafety Committee prior approval. When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV–B–3, *Biological Safety Officer*). When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human research participants, the institution must ensure that the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary). Institutional Biosafety Committee approval must be obtained from the clinical trial site.

Note: Individuals, corporations, and institutions not otherwise covered by the *NIH Guidelines,* are encouraged to adhere to the standards and procedures set forth in Sections I through IV (see Section IV–D, *Voluntary Compliance.* The policy and procedures for establishing an Institutional Biosafety Committee under *Voluntary Compliance,* are specified in Section IV–D–2, *Institutional Biosafety Committee Approval*).

Section IV–B–2–b–(1) will be amended as follows:

Section IV–B–2–b–(1). Reviewing recombinant or synthetic nucleic acid molecule research conducted at or sponsored by the institution for compliance with the *NIH Guidelines* as specified in Section III, *Experiments Covered by the NIH Guidelines,* and approving those research projects that are found to conform with the *NIH Guidelines.* This review shall include: (i) Independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant or synthetic nucleic acid molecule research; (iii) for recombinant or synthetic nucleic acid molecule research involving human research participants, assessment focused on biosafety issues (*e.g.,* administration, shedding). IBC oversight may conclude after the last participant is administered the final dose of product. However, IBCs may choose to establish other end points for oversight, based on their biosafety assessment of the proposed research.

Section IV–B–2–b–(8) will be amended as follows:

Section IV–B–2–b–(8). The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the *NIH Guidelines* until NIH establishes the containment requirement.

Section IV–B–6 will be amended as follows:

Section IV–B–6. Human Gene Transfer Expertise

When the institution participates in or sponsors recombinant or synthetic nucleic acid molecule research involving human research participants, the institution must ensure that the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary).

Section IV–B–7 will be amended as follows:

Section IV–B–7. Principal Investigator (PI)

On behalf of the institution, the Principal Investigator is responsible for full compliance with the *NIH Guidelines* in the conduct of recombinant or synthetic nucleic acid molecule research.

Section IV–B–7–b–(6) will be deleted in its entirety.

Section IV–B–7–e–(5) will be deleted in its entirety.

Section IV–C will be amended as follows:

Section IV–C. Responsibilities of the National Institutes of Health (NIH)

Section IV–C–1. NIH Director

The NIH Director is responsible for: (i) Establishment of the *NIH Guidelines,* (ii) oversight of their implementation, and (iii) their final interpretation. The NIH Director has responsibilities under the *NIH Guidelines* that involve OSP. OSP's responsibilities under the *NIH Guidelines* are administrative. In certain circumstances, there is specific opportunity for public comment with published response prior to final action.

Section IV–C–1–a. General Responsibilities

The NIH Director is responsible for:

Section IV–C–1–a–(1). Promulgating requirements as necessary to implement the *NIH Guidelines;*

Section IV–C–1–a–(2). Establishing and maintaining NIH OSP to carry out the responsibilities defined in Section IV–C–2, *Office of Science Policy;*

Section IV–C–1–a–(3). Conducting and supporting training programs in laboratory safety for Institutional Biosafety Committee members, Biological Safety Officers and other institutional experts (if applicable), Principal Investigators, and laboratory staff.

Section IV–C–1–b. Specific Responsibilities

In carrying out the responsibilities set forth in this section, the NIH Director or a designee shall weigh each proposed

action through appropriate analysis and consultation to determine whether it complies with the *NIH Guidelines* and presents no significant risk to health or the environment.

Section IV–C–1–b–(1). Major Actions

To execute *Major Actions,* the NIH Director shall provide an opportunity for public and Federal agency comment. The NIH Director's decision/recommendation (at his/her discretion) may be published in the **Federal Register** for a minimum of 15 days of comment before final action is taken. The NIH Director's final decision/recommendation, along with responses to public comments, shall be published in the **Federal Register**. Institutional Biosafety Committee Chairs shall be notified of the following decisions:

Section IV–C–1–b–(1)–(a). Changing containment levels for types of experiments that are specified in the *NIH Guidelines* when a *Major Action* is involved;

Section IV–C–1–b–(1)–(b). Assigning containment levels for types of experiments that are not explicitly considered in the *NIH Guidelines* when a *Major Action* is involved;

Section IV–C–1–b–(1)–(c). Promulgating and amending a list of classes of recombinant or synthetic nucleic acid molecules to be exempt from the *NIH Guidelines* because they consist entirely of DNA segments from species that exchange DNA by known physiological processes or otherwise do not present a significant risk to health or the environment;

Section IV–C–1–b–(1)–(d). Permitting experiments specified by Section III–A, *Experiments that Require NIH Director Approval and Institutional Biosafety Committee Approval Before Initiation;*

Section IV–C–1–b–(1)–(e). Certifying new host-vector systems with the exception of minor modifications (*e.g.,* those of minimal or no consequence to the properties relevant to containment) of already certified systems (the standards and procedures for certification are described in Appendix I–II, *Certification of Host-Vector Systems;* and

Section IV–C–1–b–(1)–(f). Adopting other changes in the *NIH Guidelines.*

Section IV–C–1–b–(2). Minor Actions

NIH OSP shall carry out certain functions as delegated to it by the NIH Director (see Section IV–C–2, *Office of Science Policy*). *Minor Actions* will be transmitted to Institutional Biosafety Committee Chairs:

Section IV–C–1–b–(2)–(a). Changing containment levels for experiments that are specified in Section III, *Experiments Covered by the NIH Guidelines* (except when a *Major Action* is involved);

Section IV–C–1–b–(2)–(b). Assigning containment levels for experiments not explicitly considered in the *NIH Guidelines;*

Section IV–C–1–b–(2)–(c). Revising the *Classification of Etiologic Agents* for the purpose of these *NIH Guidelines* (see Section V–A, *Footnotes and References of Sections I–IV*);

Section IV–C–1–b–(2)–(d). Interpreting the *NIH Guidelines* for experiments to which the *NIH Guidelines* do not specifically assign containment levels;

Section IV–C–1–b–(2)–(e). Setting containment under Sections III–D–1–d, *Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems,* and III–D–2–b, *Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems;*

Section IV–C–1–b–(2)–(f). Approving minor modifications of already certified host-vector systems (the standards and procedures for such modifications are described in Appendix I–II, *Certification of Host-Vector Systems*);

Section IV–C–1–b–(2)–(g). Decertifying already certified host-vector systems;

Section IV–C–1–b–(2)–(h). Adding new entries to the list of molecules toxic for vertebrates (see Appendix F, *Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*); and

Section IV–C–1–b–(2)–(i). Determining appropriate containment conditions for experiments according to case precedents developed under Section IV–C–1–b–(2)–(c).

Section IV–C–2. Recombinant DNA Advisory Committee (RAC) will be deleted in its entirety.

Section IV–C–3 will be amended as follows:

Section IV–C–2. Office of Science Policy (OSP)

OSP shall serve as a focal point for information on recombinant or synthetic nucleic acid molecule activities and provide advice to all within and outside NIH including institutions, Biological Safety Officers, Principal Investigators, Federal agencies, state and local governments, and institutions in the private sector. OSP shall carry out such other functions as may be delegated to it by the NIH Director. OSP's responsibilities include (but are not limited to) the following:

Section IV–C–2–a. Reviewing and approving experiments involving the cloning of genes encoding for toxin molecules that are lethal for vertebrates at an LD_{50} of less than or equal to 100 nanograms per kilogram body weight in organisms other than *Escherichia coli* K–12 (see Section III–B–1, *Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight,* Appendix F, *Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*);

Section IV–C–2–b. Publishing in the **Federal Register**, as needed;

Section IV–C–2–c. Reviewing and approving the membership of an institution's Institutional Biosafety Committee, and where it finds the Institutional Biosafety Committee meets the requirements set forth in Section IV–B–2, *Institutional Biosafety Committee (IBC),* giving its approval to the Institutional Biosafety Committee membership.

Section IV–D–5–a will be amended as follows:

Section IV–D–5–a. General

In general, the Freedom of Information Act requires Federal agencies to make their records available to the public upon request. However, this requirement does not apply to, among other things, ''trade secrets and commercial or financial information that is obtained from a person and that is privileged or confidential.'' Under 18 U.S.C. 1905, it is a criminal offense for an officer or employee of the U.S. or any Federal department or agency to publish, divulge, disclose, or make known ''in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, (or) processes . . . of any person, firm, partnership, corporation, or association.'' This provision applies to all employees of the Federal Government, including special Government employees.

In submitting to NIH for purposes of voluntary compliance with the *NIH Guidelines,* an institution may designate those items of information which the institution believes constitute trade secrets, privileged, confidential, commercial, or financial information. If NIH receives a request under the Freedom of Information Act for information so designated, NIH will promptly contact the institution to secure its views as to whether the information (or some portion) should be

released. If NIH decides to release this information (or some portion) in response to a Freedom of Information request or otherwise, the institution will be advised and the actual release will be delayed in accordance with 45 Code of Federal Regulations, Section 5.65(d) and (e).

None of the other sub-sections under Section IV. Roles and Responsibilities will be amended.

Section V will be amended as follows:

Section V. Footnotes and References of Sections I Through IV

Section V–A. The NIH Director may revise the classification for the purposes of the *NIH Guidelines* (see Section IV–C–1–b–(2)–(e), *Minor Actions*). The revised list of organisms in each Risk Group is reprinted in Appendix B, *Classification of Human Etiologic Agents on the Basis of Hazard.*

Section V–B. Section III, *Experiments Covered by the NIH Guidelines,* describes a number of places where judgments are to be made. In all these cases, the Principal Investigator shall make the judgment on these matters as part of his/her responsibility to ''make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*'' (see Section IV–B–7–c–(1)). For cases falling under Sections III–A through III–E, *Experiments Covered by the NIH Guidelines,* this judgment is to be reviewed and approved by the Institutional Biosafety Committee as part of its responsibility to make an ''independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research'' (see Section IV–B–2–b–(1), *Institutional Biosafety Committee*). The Institutional Biosafety Committee may refer specific cases to NIH OSP as part of NIH OSP's functions to ''provide advice to all within and outside NIH'' (see Section IV–C–2).

None of the other sub-sections under Section V. Footnotes and References of Sections I Through IV will be amended.

Appendix A will be amended as follows:

Appendix A. Exemptions Under Section III–F–6—Sublists of Natural Exchangers

Certain specified recombinant or synthetic nucleic acid molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent are exempt from these *NIH Guidelines* (see Section III–F–6, *Exempt Experiments*). Institutional Biosafety Committee registration is not required for these exempt experiments. A list of such exchangers will be prepared and periodically revised by the NIH Director after appropriate notice and opportunity for public comment (see Section IV–C–1–b–(1)–(c), *NIH Director—Specific Responsibilities*). For a list of natural exchangers that are exempt from the *NIH Guidelines,* see Appendices A–I through A–VI, *Exemptions under Section III–F–6 Sublists of Natural Exchangers.* Section III–F–6, *Exempt Experiments,* describes recombinant or synthetic nucleic acid molecules that are: (1) Composed entirely of DNA segments from one or more of the organisms within a sublist, and (2) to be propagated in any of the organisms within a sublist (see *Bergey's Manual of Systematic Bacteriology;* 2nd edition, Springer-Verlag; New York, NY). Although these experiments are exempt, it is recommended that they be performed at the appropriate biosafety level for the host or recombinant/synthetic organism (see *Biosafety in Microbiological and Biomedical Laboratories,* 5th edition, 2009, U.S. DHHS, Public Health Service, Centers for Disease Control and Prevention, and National Institutes of Health).

None of the sub-sections under Appendix A. Exemptions Under III–F–6—Sublists of Natural Exchangers will be amended.

Appendix B will be amended as follows:

Appendix B. Classification of Human Etiologic Agents on the Basis of Hazard

This appendix includes those biological agents known to infect humans as well as selected animal agents that may pose theoretical risks if inoculated into humans. Included are lists of representative genera and species known to be pathogenic; mutated, recombined, and non-pathogenic species and strains are not considered. Non-infectious life cycle stages of parasites are excluded.

This appendix reflects the current state of knowledge and should be considered a resource document. Included are the more commonly encountered agents and is not meant to be all-inclusive. Information on agent risk assessment may be found in the *Agent Summary Statements* of the CDC/NIH publication, Biosafety in Microbiological and Biomedical Laboratories (see Sections V–C, V–D, V–E, and V–F, *Footnotes and References of Sections I through IV*). Further guidance on agents not listed in Appendix B may be obtained through: Centers for Disease Control and Prevention, Biosafety Branch, Atlanta, Georgia 30333, Phone: (404) 639–3883, Fax: (404) 639–2294; National Institutes of Health, Division of Safety, Bethesda, Maryland 20892, Phone: (301) 496–1357; Biosafety Manager, National Animal Disease Center, U.S. Department of Agriculture—ARS, Ames, Iowa 50010, Phone: (515) 337–7772.

None of the sub-sections under Appendix B. Classification of Human Etiologic Agents on the Basis of Hazard nor Table 1 will be amended.

Appendix C will be amended as follows:

Appendix C. Exemptions Under Section III–F–8

Section III–F–8 states that exempt from these *NIH Guidelines* are ''those that do not present a significant risk to health or the environment (see Section IV–C–1–b–(1)–(c), *Major Actions*), as determined by the NIH Director following appropriate notice and opportunity for public comment. See Appendix C, *Exemptions under Sections III–F–8,* for other classes of experiments which are exempt from the *NIH Guidelines.*'' The following classes of experiments are exempt under Section III–F–8:

Appendix C–IX–A. will be amended as follows:

Appendix C–IX–A. The NIH Director may revise the classification for the purposes of these *NIH Guidelines* (see Section IV–C–1–b–(2)–(b), *Minor Actions*). The revised list of organisms in each Risk Group is located in Appendix B.

None of the other sub-sections under Appendix C. Exemptions Under Section III–F–8 will be amended.

Appendix D will be amended as follows:

Appendix D. Major Actions Taken Under The *NIH Guidelines*

As noted in the subsections of Section IV–C–1–b–(1), the Director, NIH, may take certain actions with regard to the *NIH Guidelines.* (Entries up to and including D–118 were approved using a process that involved the Recombinant DNA Advisory Committee.) Some of the actions taken to date include the following:

None of the sub-sections under Appendix D. Major Actions Taken Under The NIH Guidelines will be amended.

Appendix I–II will be amended as follows:

Appendix I–II. Certification of Host-Vector Systems

Appendix I–II–A. Responsibility

Host-Vector 1 systems (other than *Escherichia coli* K–12) and Host-Vector 2 systems may not be designated as such until they have been certified by the NIH Director. Requests for certification of host-vector systems may be submitted to the Office of Science Policy, National Institutes of Health, preferably by email to: *NIHGuidelines@od.nih.gov*; additional contact information is also available here and on the OSP website (*www.osp.od.nih.gov*). Proposed host-vector systems will be reviewed based on the construction, properties, and testing of the proposed host-vector system by *ad hoc* experts. The NIH Director is responsible for certification of host-vector systems. Minor modifications to existing host-vector systems (*i.e.,* those that are of minimal or no consequence to the properties relevant to containment) may be certified by the NIH Director (see Section IV–C–1–b–(2)–(f), *Minor Actions*). Once a host-vector system has been

certified by the NIH Director, a notice of certification will be sent by NIH OSP to the applicant and to the Institutional Biosafety Committee Chairs. A list of all currently certified host-vector systems is available from the Office of Science Policy, National Institutes of Health, preferably by submitting a request for this information to: *NIHGuidelines@od.nih.gov*; additional contact information is also available here and on the OSP website (*www.osp.od.nih.gov*). The NIH Director may rescind the certification of a host-vector system (see Section IV–C–1–b–(2)–(g), *Minor Actions*). If certification is rescinded, NIH will instruct investigators to transfer cloned DNA into a different system or use the clones at a higher level of physical containment level, unless NIH determines that the already constructed clones incorporate adequate biological containment. Certification of a host-vector system does not extend to modifications of either the host or vector component of that system. Such modified systems shall be independently certified by the NIH Director. If modifications are minor, it may only be necessary for the investigator to submit data showing that the modifications have either improved or not impaired the major phenotypic traits on which the containment of the system depends. Substantial modifications to a certified host-vector system require submission of complete testing data.

Appendix I–II–B. Data To Be Submitted for Certification

Appendix I–II–B–1. Host-Vector 1 Systems Other Than *Escherichia coli* K–12

The following types of data shall be submitted, modified as appropriate for the particular system under consideration: (i) A description of the organism and vector; the strain's natural habitat and growth requirements; its physiological properties, particularly those related to its reproduction, survival, and the mechanisms by which it exchanges genetic information; the range of organisms with which this organism normally exchanges genetic information and the type of information exchanged; and any relevant information about its pathogenicity or toxicity; (ii) a description of the history of the particular strains and vectors to be used, including data on any mutations which render this organism less able to survive or transmit genetic information; and (iii) a general description of the range of experiments contemplated with emphasis on the need for developing such an Host-Vector 1 system.

Appendix I–II–B–2. Host-Vector 2 Systems

Investigators planning to request Host-Vector 2 systems certification may obtain instructions from NIH OSP concerning data to be submitted (see Appendices I–III–N and O, *Footnotes and References of Appendix I*). In general, the following types of data are required: (i) Description of construction steps with indication of source, properties, and manner of introduction of genetic traits; (ii) quantitative data on the stability of genetic traits that contribute to the containment of the system; (iii) data on the survival of the host-vector system under non-permissive laboratory conditions designed to represent the relevant natural environment; (iv) data on transmissibility of the vector and/or a cloned DNA fragment under both permissive and non-permissive conditions; (v) data on all other properties of the system which affect containment and utility, including information on yields of phage or plasmid molecules, ease of DNA isolation, and ease of transfection or transformation; and (vi) in some cases, the investigator may be asked to submit data on survival and vector transmissibility from experiments in which the host-vector is fed to laboratory animals or one or more human subjects. Such *in vivo* data may be required to confirm the validity of predicting *in vivo* survival on the basis of *in vitro* experiments. Data shall be submitted to the Office of Science Policy, National Institutes of Health, preferably by email to: *NIHGuidelines@od.nih.gov*; additional contact information is also available here and on the OSP website (*www.osp.od.nih.gov*). Investigators are encouraged to publish their data on the construction, properties, and testing of proposed Host-Vector 2 systems prior to consideration of the system by NIH. Specific instructions concerning the submission of data for proposed *Escherichia coli* K–12 Host-Vector 2 system (EK2) involving either plasmids or bacteriophage in *Escherichia coli* K–12, are available from the Office of Science Policy, National Institutes of Health, preferably by submitting a request for this information to: *NIHGuidelines@od.nih.gov*; additional contact information is also available here and on the OSP website (*www.osp.od.nih.gov*).

None of the other sub-sections under Appendix I. Biological Containment will be amended.

Appendix L. Gene Therapy Policy Conferences (GTPCS) will be deleted in its entirety.

Appendix M. Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant or Synthetic Nucleic Acid Molecules into One or More Human Research Participants (Points to Consider) will be deleted in its entirety.

Dated: April 10, 2019.

Lawrence A. Tabak,

Principal Deputy Director, National Institutes of Health.

[FR Doc. 2019–08462 Filed 4–25–19; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HOMELAND SECURITY

Coast Guard

[Docket No. USCG–2019–0139]

Certificate of Alternative Compliance for the Tug RANDY McCRANEY

AGENCY: Coast Guard, DHS.

ACTION: Notification of issuance of a certificate of alternative compliance.

SUMMARY: The Coast Guard announces that the Fifth District, Chief of Prevention Division has issued a certificate of alternative compliance from the International Regulations for Preventing Collisions at Sea, 1972 (72 COLREGS), for the towing vessel RANDY McCRANEY, Official Number (O.N.) 1292293, Master Boat Builders Hull Number 459. We are issuing this notice because its publication is required by statute. Due to its construction, purpose and service, the towing vessel RANDY McCRANEY cannot fully comply with the light, shape, or sound signal provisions of the 72 COLREGS without interfering with the vessel's design and construction. This notification of issuance of a certificate of alternative compliance promotes the Coast Guard's marine safety mission.

DATES: The Certificate of Alternative Compliance was issued on March 15, 2019.

FOR FURTHER INFORMATION CONTACT: For information or questions about this notice call or email LCDR Ronaydee M. Marquez, District Five, Asst. Chief, Inspections and Investigations, U.S. Coast Guard; telephone: 757–398–6682, email: *Ronaydee.M.Marquez@uscg.mil.*

SUPPLEMENTARY INFORMATION: The United States is signatory to the International Maritime Organization's International Regulations for Preventing Collisions at Sea, 1972 (72 COLREGS), as amended. The special construction or purpose of some vessels makes them unable to comply with the light, shape, or sound signal provisions of the 72 COLREGS. Under statutory law, however, specified 72 COLREGS provisions are not applicable to a vessel of special construction or purpose if the Coast Guard determines that the vessel cannot comply fully with those requirements without interfering with the special function of the vessel.[1]

The owner, builder, operator, or agent of a special construction or purpose vessel may apply to the Coast Guard District Office in which the vessel is being built or operated for a determination that compliance with alternative requirements is justified,[2] and the Chief of the Prevention Division would then issue the applicant a certificate of alternative compliance (COAC) if he or she determines that the vessel cannot comply fully with 72 COLREGS light, shape, and sound signal

[1] 33 U.S.C. 1605.

[2] 33 CFR 81.5.