

**Proposed Revisions
to the *NIH Guidelines:*
Responses to Public
Comments**

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Proposed Revisions to Section I-B Definition

In the context of the *NIH Guidelines*, recombinant and synthetic nucleic acids are defined as:

- (i) Recombinant nucleic acid molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell,
- (ii) **Synthetic nucleic acid molecules that are chemically, or by other means, synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules**
- (iii) molecules that result from the replication of those described in (i) or (ii) above.

Proposed Revisions to Section I-A Purpose

- The purpose of the NIH Guidelines is to specify the practices 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 (bind) with naturally occurring nucleic acid molecules, and (iii) cells, organisms and viruses containing such molecules

Proposed Revision to III-F-1

Section III-F-1

Those synthetic nucleic acids that:

- a) can neither replicate nor generate nucleic acids that can replicate in a living cell, and
- b) are not designed to integrate into DNA, and
- c) do not produce a toxin that is lethal for vertebrates at an LD50 < 100 nanograms, and
- d) are not deliberately transferred into one or more human research participants (see Section III-C and Appendix M).

Proposed Addition to Appendix M (Human Gene Transfer)

Appendix M-VI-B

Human studies in which synthetic DNA nucleotides are deliberately transferred into one or more human research participants are exempt from Appendix M-1, *Requirements for Protocol Submission, Review and Reporting- Human Gene Transfer* if the DNA nucleotides meet the following criteria:

Proposed Addition to Appendix M (Human Gene Transfer)

Continued...

- Contain fewer than 100 DNA nucleotides in total (single stranded, double stranded, or partially double stranded); AND
- Unable to integrate into the genome (i.e. do not contain known viral vector, transposable element or other known sequences designed to promote integration of the molecule into the genome) AND

Proposed Addition to Appendix M (Human Gene Transfer)

Continued...

- Cannot replicate in cells (i.e. do not contain elements known to interact with either DNA or RNA polymerase); AND
- Do not comprise a gene (i.e. do not contain promoter/enhancer elements, transcription initiation elements or polyadenylation sequences designed to enable the molecule to be transcribed into mRNA)
- And is not intended to permanently modify the genome

Proposed Revisions to 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 use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by RAC.
- Consideration should be given 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 pediatric populations and pregnant women.

Proposed Revisions to Section III-A-1-a

- OBA will provide, following consultation as needed, a determination regarding whether a specific line of research involving the deliberate transfer of a drug resistance trait falls under Section III-A-1-a and therefore requires RAC review and NIH Director approval prior to initiation. An IBC may consult OBA regarding experiments that do not meet the requirements of Section III-A-1-a but nonetheless raise important public health issues and OBA will consult as needed with one or more experts, which may include the RAC.

Section III-E-1

Proposed Revisions

Recombinant and synthetic nucleic acid molecules containing:

- 1) no more than half of the genome of any RG3 or RG4 eukaryotic virus OR
- 2) nucleic acid molecules from any Risk Group eukaryotic virus containing a complete deletion in one or more essential viral capsid, envelope or polymerase genes required for cell-to-cell transmission of viral nucleic acids (all viruses from a single family being considered identical) . . . may be propagated and maintained in cells in tissue culture using BL1 containment (as defined in Appx G) provided there is evidence that the resulting nucleic acids in these cells are not capable of producing a replication competent virus. For such experiments, it must be demonstrated that the cells lack helper virus for specific families of defective viruses being used . . .

Section III-E-1

Proposed Revisions

For retroviruses and lentiviruses that have the potential to transduce human cells and cause insertional mutagenesis, a minimum of BL2 containment is required.