Recent Amendments to the *NIH Guidelines*

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Recent Amendments to the *NIH Guidelines*

- **Research with synthetic nucleic acids**
  - **What is covered and what isn't**
  - **Risk assessment**
- **Transfer of drug resistance traits to microorganisms (Section III-A-1-a)**

Research with Synthetic Nucleic Acids

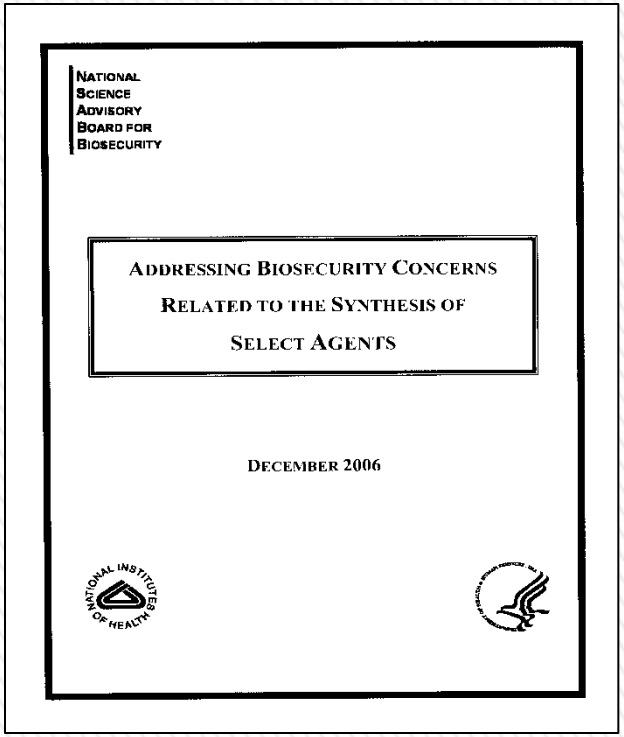
Impetus for Amending the Scope of the *NIH Guidelines*

- **Recognition that appropriate biosafety containment of an agent is critical regardless of the technology used to generate that agent (i.e., recombinant or synthetic).**

Impetus for Amending the Scope of the *NIH Guidelines*

- **Capture the same products made by synthetic techniques that were previously covered under the *NIH Guidelines* made with recombinant DNA techniques, provided the same biosafety concerns are raised.**

National Science Advisory Board for Biosecurity (NSABB) Report



http://oba.od.nih.gov/biosecurity/biosecurity_documents.html

NSABB Findings

- **Some practitioners of synthetic genomics are:**
  - **Educated in disciplines that do not routinely entail formal training in biosafety; and**
  - **Uncertain about when to consult an Institutional Biosafety Committee (IBC).**

NSABB Findings

- There is a “need to examine the language and implementation of current biosafety guidance to ensure that such guidelines and regulations provide adequate guidance for working with synthetically derived DNA and are understood by all those working in areas addressed by the guidelines.”

NIH Guidelines Oct. 2011 Language

- ***NIH Guidelines*** **define Recombinant DNA as:**
  - **Molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or**
  - **Molecules that result from the replication of those described above**

New Scope of the *NIH Guidelines*

- **Explicit inclusion of certain basic and clinical research with nucleic acid molecules created solely by synthetic means**
  - **Provisions for exemption of certain classes of research with synthetic nucleic acids paralleling the existing exemptions for recombinant DNA**

New Title of the *NIH Guidelines*

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Specific Sections of the *NIH Guidelines* That Have Been Amended

Section I.	**Scope of the *NIH Guidelines***
Section I-B.	**Definition of Recombinant DNA**
Section I-C.	**General Applicability**
Section II-A-3.	**Comprehensive Risk Assessment**
Section III-C.	**Experiments involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA Derived from Recombinant DNA, into One or More Human Research Participants**
Section III-F.	**Exempt Experiments**
Section IV-A.	**Policy**

Section I-A of the *NIH Guidelines*

- **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 with naturally occurring nucleic acid molecules, and
  (iii) cells, organisms and viruses containing such molecules.

Section I-B of the *NIH Guidelines*

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

  (i) molecules that a) are constructed by joining nucleic acid molecules and b) can replicate in a living cell, i.e. recombinant nucleic acids;

  (ii) 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, i.e. synthetic nucleic acids; or

  (iii) molecules that result from the replication of those described in (i) or (ii) above.

Section III-C-1 of the *NIH Guidelines*

- **Human gene transfer is the deliberate transfer into human research participants of either:**
  - **Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or**
  - **Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:**

continued …

Section III-C-1 of the *NIH Guidelines*

… continued

- **Contain more than 100 nucleotides; or**
- **Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or**
- **Have the potential to replicate in a cell; or**
- **Can be translated or transcribed.**

Section III-F-1 of the *NIH Guidelines*

- **Exempts those synthetic nucleic acids that:**

(1) can neither replicate nor generate nucleic acids that can replicate in any living cell (e.g., oligonucleotides or other synthetic nucleic acids that do not contain an origin of replication or contain elements known to interact with either DNA or RNA polymerase), and
(2) are not designed to integrate into DNA, and
(3) do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram body weight.

Section III-F-1 of the *NIH Guidelines*

Note: **If a synthetic nucleic acid is deliberately transferred into one or more human research participants and meets the amended criteria of Section III-C, it is not exempt under the *NIH Guidelines*.**

Section III-F-2 of the *NIH Guidelines*

- **Exempts the following experiments:**
  - **Those that are not in organisms, cells or viruses and that have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes.**

Other Changes

- **Previous section III-F-2 has been renumbered to III-F-3 etc.**
- **Throughout the *NIH Guidelines*, the term “recombinant DNA molecules” will be replaced with “recombinant or synthetic nucleic acids,” which will encompass research with either recombinant or synthetic or both types of nucleic acids.**

Other Changes

- **As a result, the *NIH Guidelines* apply (unless otherwise exempted by other sections of the *NIH Guidelines*, e.g. III-F) to both recombinant and synthetically derived nucleic acids, including those that are chemically or otherwise modified analogs of nucleotides (e.g., morpholinos).**

Is the Synthesis of Naturally Occurring Organisms Covered?

- **No - Section III-F-3 exempts experiments that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature.**

Is the Synthesis of Naturally Occurring Organisms Covered?

- **Note that this exemption is limited to those nucleic acid sequences from organisms that exist outside of a laboratory setting. Research with nucleic acid sequences for organisms that do not currently exist in nature outside of a laboratory, for example, an identical copy of the 1918 H1N1 influenza virus is <u>not</u> exempt**

Is the Chemical Synthesis of Nucleic Acid Molecules Subject to the *NIH Guidelines*?

- **No, the *NIH Guidelines* do not cover the chemical synthesis of nucleic acids. While the scope of the *NIH Guidelines* refers to "constructing" nucleic acids, the *NIH Guidelines* exempts research with nucleic acids that are not contained in cells, organisms or viruses. Therefore, the chemical synthesis of nucleic acids is exempt. The *NIH Guidelines* only apply once synthetic nucleic acids are placed in a biological system.**

Risk Assessments For Synthetic Nucleic Acid Research

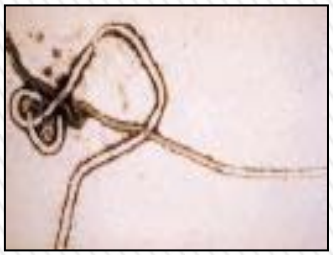
Risk Assessment - *NIH Guidelines*

RG 1	RG 2	RG 3	RG 4
Agents that are not associated with disease in healthy adult humans	**Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available**	**Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk but low community risk)**	**Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available (high individual risk and high community risk)**

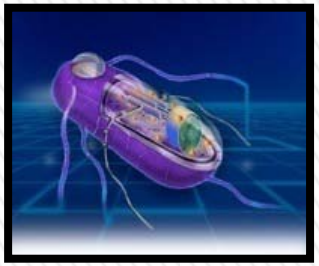
Risk Assessment for Research with Synthetic NA

Available data to support a biosafety risk assessment

Known Agents



Novel/ Uncharacterized Agents



Risk Assessment for Research with Synthetic NA

- **Risk assessment for synthetic nucleic acids is not fundamentally different from that for recombinant DNA research; however**
  - **As the technology moves forward, chimeras may be generated for which the parent organism is not obvious**
  - **Factors to be considered:**
    - **Percent of genome contributed by each of multiple parental agents**
    - **Predicted function or intended purpose of each sequence**

Risk Assessment for Research with Synthetic NA

- In the absence of data indicating otherwise, assume the sequence will function as it does in the original host
- Consider the possibility of novel synergism between sequences and transgenes resulting in an organism whose risk profile is higher than that of the contributing sequences or organisms

Transfer of Drug Resistance Traits to Microorganisms (Section III-A-1-a)

Section III-A-1-a

- **The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture**
- **Requires RAC review and NIH Director approval.**

Section III-A-1-a

- Criteria for determining whether an experiment requires review under III-A-1-a has been retained
- Additional clarifying language has been added regarding the assessment of whether a drug is therapeutically useful

Specific Sections of the *NIH Guidelines* That Have Been Amended

Section III-A-1-a.	**Major Actions under the *NIH Guidelines***
Section III-B.	**Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval before Initiation**

Section III-A-1-a of the *NIH Guidelines*

- **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.**

Section III-A-1-a of the *NIH Guidelines*

- **At the request of an Institutional Biosafety Committee, NIH/OBA 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 RAC review and NIH Director approval.**

Section III-A-1-a of the *NIH Guidelines*

- **An Institutional Biosafety Committee may also consult with NIH/OBA regarding experiments that do not meet the requirements of Section III-A-1-a but nonetheless raise important public health issues. NIH/OBA will consult, as needed, with one or more experts, which may include the RAC.**

Section III-B-2 of the *NIH Guidelines*

- **Section III-B-2. Experiments that have been Approved (under Section III-A-1-a) as Major Actions under the *NIH Guidelines***
  - **NIH/OBA may determine that a proposed experiment is equivalent to an experiment that has previously been approved by the NIH Director as a Major Action, including experiments approved prior to implementation of these changes.**

Section III-B-2 of the *NIH Guidelines* (continued)

- **An experiment will only be considered equivalent if, as determined by NIH/OBA, there are no substantive differences and pertinent information has not emerged since submission of the initial III-A-1-a experiment.**
- **If such a determination is made by NIH/OBA, these experiments will not require review and approval under Section III-A-1-a.**

When do the Requirements Under the Amended *NIH Guidelines* Go Into Effect?

- **Effective six months after the date of publication of the changes in the Federal Register (September 5, 2012):**
  - **All ongoing and proposed experiments that will be newly subject to the amended *NIH Guidelines* will need to be registered by the Principal Investigator with the IBC by March 5, 2013**

Implementation of Amended *NIH Guidelines*

- **Institutions should use this time to develop new procedures and reach out to investigators performing research that is not currently covered under the *NIH Guidelines*, but will be covered in March 2013**
- **Composition of the IBC does not need to change, but Institutions may choose to add to the membership**

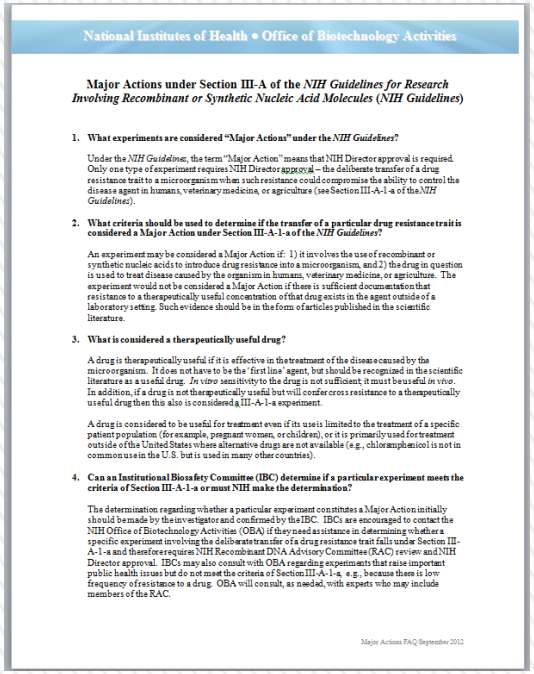
Additional Resources

- **Additional Information on these changes can be found in the published Federal Register Notice 77 FR 54584 (September 5, 2012) which is available at:**

http://oba.od.nih.gov/rdna/nih_guidelines_oba.html

Additional Resources

- **OBA Frequently Asked Questions (FAQ)**



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Major Actions under Section III-A of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (*NIH Guidelines*)

1. **What experiments are considered "Major Actions" under the *NIH Guidelines*?**

   Under the *NIH Guidelines*, the term "Major Action" means that NIH Director approval is required. Only one type of experiment requires NIH Director approval – the deliberate transfer of a drug resistance trait to a microorganism when such resistance could compromise the ability to control the disease agent in humans, veterinary medicine, or agriculture (see Section III-A-1-a of the *NIH Guidelines*).

2. **What criteria should be used to determine if the transfer of a particular drug resistance trait is considered a Major Action under Section III-A-1-a of the *NIH Guidelines*?**

   An experiment may be considered a Major Action if: 1) it involves the use of recombinant or synthetic nucleic acids to introduce drug resistance into a microorganism, and 2) the drug in question is used to treat disease caused by the organism in humans, veterinary medicine, or agriculture. The experiment would not be considered a Major Action if there is sufficient documentation that resistance to a therapeutically useful concentration of that drug exists in the agent outside of a laboratory setting. Such evidence should be in the form of articles published in the scientific literature.

3. **What is considered a therapeutically useful drug?**

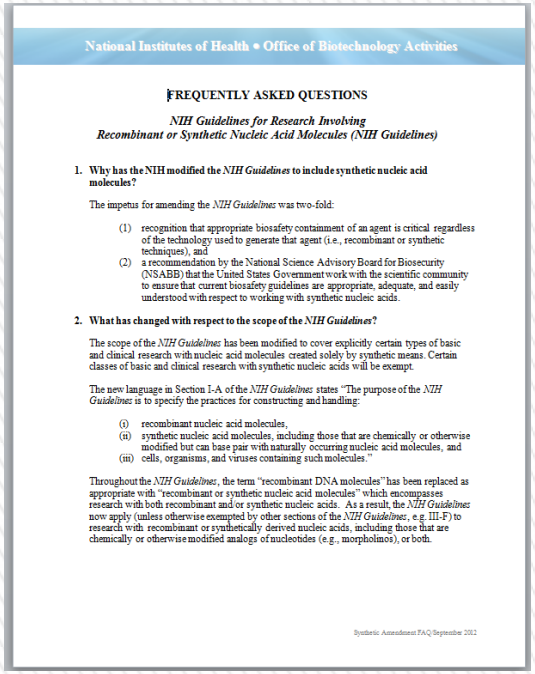
   A drug is therapeutically useful if it is effective in the treatment of the disease caused by the microorganism. It does not have to be the 'first line' agent, but should be recognized in the scientific literature as a useful drug. *In vitro* sensitivity to the drug is not sufficient; it must be useful *in vivo*. In addition, if a drug is not therapeutically useful but will confer cross resistance to a therapeutically useful drug then this also is considered a III-A-1-a experiment.

   A drug is considered to be useful for treatment even if its use is limited to the treatment of a specific patient population (for example, pregnant women, or children), or it is primarily used for treatment outside of the United States where alternative drugs are not available (e.g., chloramphenicol is not in common use in the U.S. but is used in many other countries).

4. **Can an Institutional Biosafety Committee (IBC) determine if a particular experiment meets the criteria of Section III-A-1-a or must NIH make the determination?**

   The determination regarding whether a particular experiment constitutes a Major Action initially should be made by the investigator and confirmed by the IBC. IBCs are encouraged to contact the NIH Office of Biotechnology Activities (OBA) if they need assistance in determining whether a specific experiment involving the deliberate transfer of a drug resistance trait falls under Section III-A-1-a and therefore requires NIH Recombinant DNA Advisory Committee (RAC) review and NIH Director approval. IBCs may also consult with OBA regarding experiments that raise important public health issues but do not meet the criteria of Section III-A-1-a, e.g., because there is low frequency of resistance to a drug. OBA will consult, as needed, with experts who may include members of the RAC.

Major Actions FAQ/September 2012



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FREQUENTLY ASKED QUESTIONS

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

1. **Why has the NIH modified the *NIH Guidelines* to include synthetic nucleic acid molecules?**

   The impetus for amending the *NIH Guidelines* was two-fold:

   (1) recognition that appropriate biosafety containment of an agent is critical regardless of the technology used to generate that agent (i.e., recombinant or synthetic techniques), and
   (2) a recommendation by the National Science Advisory Board for Biosecurity (NSABB) that the United States Government work with the scientific community to ensure that current biosafety guidelines are appropriate, adequate, and easily understood with respect to working with synthetic nucleic acids.

2. **What has changed with respect to the scope of the *NIH Guidelines*?**

   The scope of the *NIH Guidelines* has been modified to cover explicitly certain types of basic and clinical research with nucleic acid molecules created solely by synthetic means. Certain classes of basic and clinical research with synthetic nucleic acids will be exempt.

   The new language in Section I-A of the *NIH Guidelines* states "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 with naturally occurring nucleic acid molecules, and
   (iii) cells, organisms, and viruses containing such molecules."

   Throughout the *NIH Guidelines*, the term "recombinant DNA molecules" has been replaced as appropriate with "recombinant or synthetic nucleic acid molecules" which encompasses research with both recombinant and/or synthetic nucleic acids. As a result, the *NIH Guidelines* now apply (unless otherwise exempted by other sections of the *NIH Guidelines*, e.g. III-F) to research with recombinant or synthetically derived nucleic acids, including those that are chemically or otherwise modified analogs of nucleotides (e.g., morpholinos), or both.

Synthetic Amendment FAQ/September 2012

http://oba.od.nih.gov/rdna/rdna_faq_list.html

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Questions?