

A large, 3D-rendered DNA double helix structure, colored in shades of blue and white, positioned vertically on the left side of the slide.

***NIH Guidelines for Research  
involving Recombinant  
or  
Synthetic Nucleic Acid  
Molecules***

**Proposed**

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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**





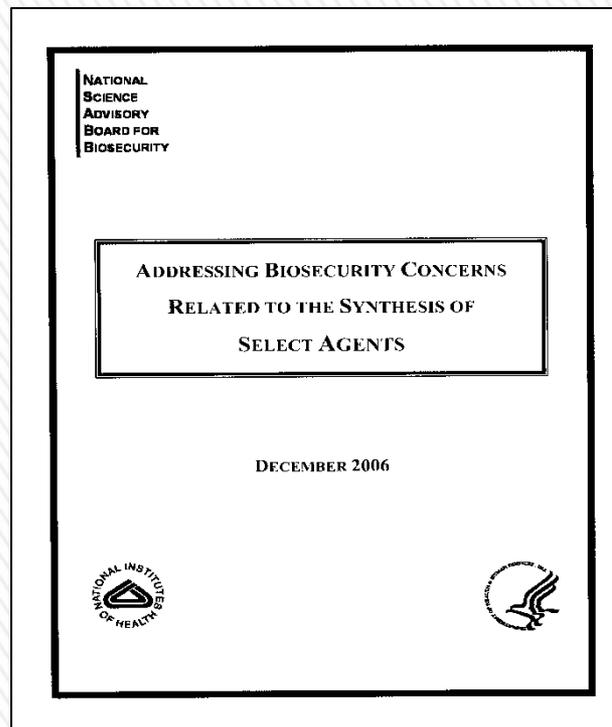
# **Impetus for amending the *NIH Guidelines***

- **Recognition that appropriate biosafety containment of an agent is critical regardless of the technology used to generate that agent (i.e., recombinant or synthetic)**
  - **Capture the same products made by synthetic techniques that were previously covered under the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, provided that the same biosafety concerns are raised**





# National Science Advisory Board for Biosecurity (NSABB) Report



[http://oba.od.nih.gov/biosecurity/biosecurity\\_documents.html](http://oba.od.nih.gov/biosecurity/biosecurity_documents.html)



# 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.”**



# Current *NIH Guidelines* *(October 2011)*



- ***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**





# **Amended NIH Guidelines (March 2013)**

- **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 research with recombinant DNA**





# Implementation of amended *NIH Guidelines*

- The amended NIH Guidelines go into effect in six months – March 2013
- 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





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

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



## **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.**





## 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.





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

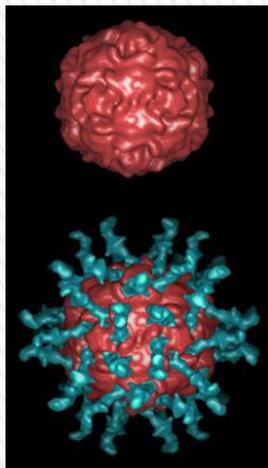
- **Exempts the following experiments:**
  - **Section III-F-2. Those that are not in organisms, cells or viruses and that have not been modified or manipulated (e.g., encapsulated into synthetic or natural vehicles) to render them capable of penetrating cellular membranes.**





# 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.**
  - **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 not exempt**





# **Exemption for Basic Research with Synthetic NA**

- **Exposure in a lab to a low dose of non-replicating synthetic nucleic acid molecules is considered low risk:**
  - **No replication even if the nucleic acid enters a cell**
  - **No ability to spread in the environment if released**
  - **Nucleic acids are not toxic in and of themselves**





## **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.**

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





# Human Gene Transfer and Synthetic Nucleic Acids

- **Delivery of synthetic nucleic acid molecules expressed by a vector (e.g. plasmid or viral vector) raises the same issues as delivery of rDNA, because the products have similar properties**
- **Short synthetic RNA or DNA delivered directly or encapsulated (e.g. nanoparticle) have distinct characteristics**
  - **Generally molecules that are too small to encode a protein**
  - **Lack ability to integrate**
  - **Lack of replication or potential for inadvertent replication due to mobilization or recombination**





## 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:**
    - **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.**





## Other Changes

- Throughout the *NIH Guidelines*, the term “recombinant DNA molecules” has been replaced with “recombinant or synthetic nucleic acids molecules,” which will encompass research with either recombinant or synthetic or both types of nucleic acids.
- 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).





# **Risk Assessments For Synthetic Nucleic Acid Research**





# Risk Assessment - *NIH Guidelines*

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



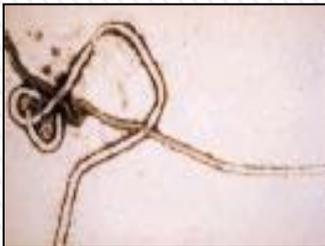


# Risk Assessment for Research with Synthetic NA

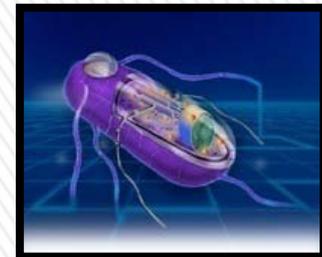
Available data to support a biosafety risk assessment



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 a Drug Resistance Trait to Microorganisms (Section III-A-1-a)**





# Current Section II-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**
- **Expedited review of “me too” experiments**





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

**Section III-A-1. Major Actions under the  
*NIH Guidelines***

**Section III-B. Experiments that  
Require NIH/OBA and  
Institutional Biosafety  
Committee Approval  
before Initiation**





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

- 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 of the *NIH Guidelines* (*Additional Clarifying Language*)**

- **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 of the *NIH Guidelines* (additional language)**

- **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. 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.**





## **New 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 experiment**
- **If such a determination is made by NIH/OBA, these experiments will not require review and approval under Section III-A-1.**





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

- **Effective six months after the date of publication in the Federal Register:**
  - **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 2013**





# **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](http://oba.od.nih.gov/rdna/nih_guidelines_oba.html)**

**OBA Frequently Asked Questions (FAQ) and Guidances**

**[http://oba.od.nih.gov/rdna/rdna\\_faq\\_list.html](http://oba.od.nih.gov/rdna/rdna_faq_list.html)**





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# Questions?

