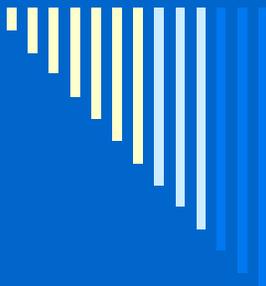


Synthetic Biology and the *NIH Guidelines for Experiments Involving Recombinant DNA Molecules*

March 11, 2008





Impetus for Review of Synthetic Genomics

DNA synthesis technology is rapidly advancing. Can be used to synthesize partial or, in some circumstances, whole genomes *de novo*, without needing access to natural sources of organisms or their nucleic acids.

+

Open availability of DNA sequence data of pathogens

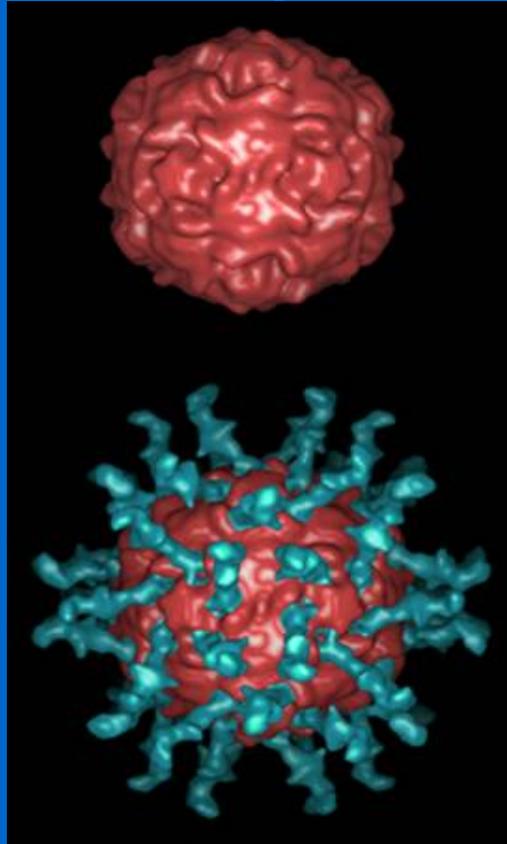
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Concerns that this technology and information could be misused to make dangerous pathogens to threaten public health

"Synthetic Polio Virus Made from Mail-Order Kits"

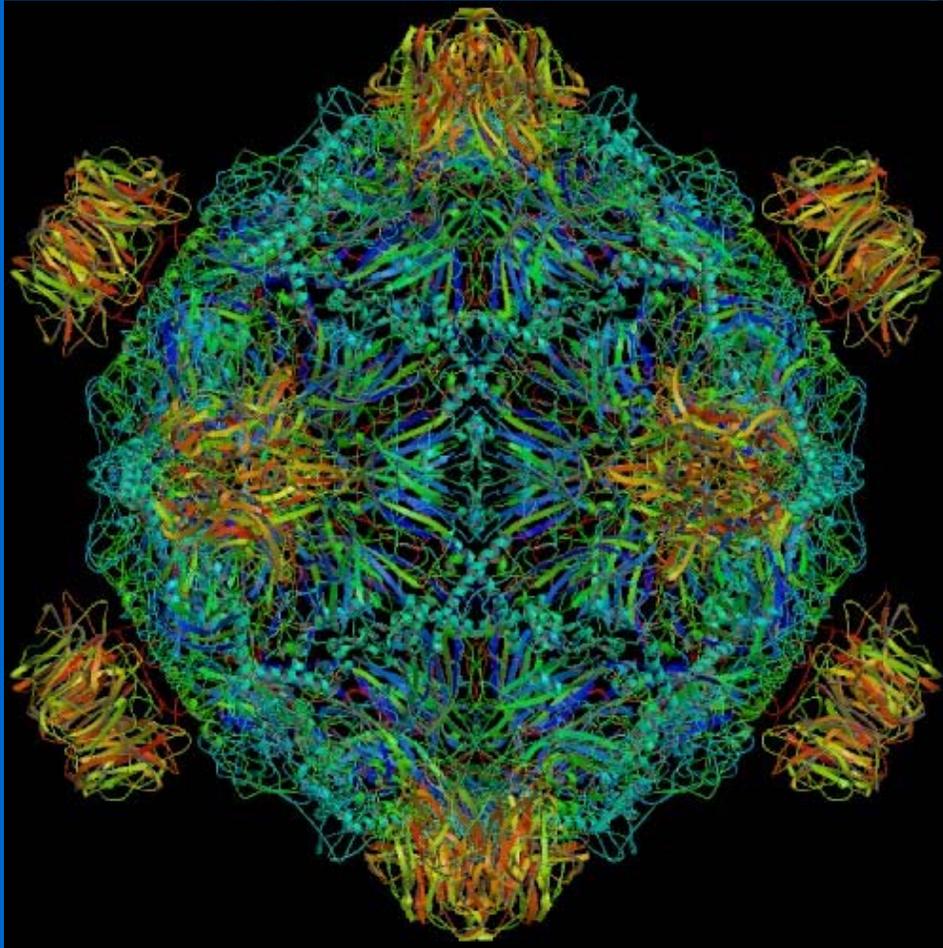
CELL – July, 2002

- Eckard Wimmer synthesized entire polio genome using readily available reagents and well-established molecular biology techniques
- Synthetic virus was infectious, capable of replication, and pathogenic.
- In vitro synthesis took 3 years to complete
- Application could lead to benefits for medicine, such as rebuilding other viruses in a weakened form to help devise vaccines.



“Virus Built from Scratch in Two Weeks”

New method accelerates prospect of designer microbes

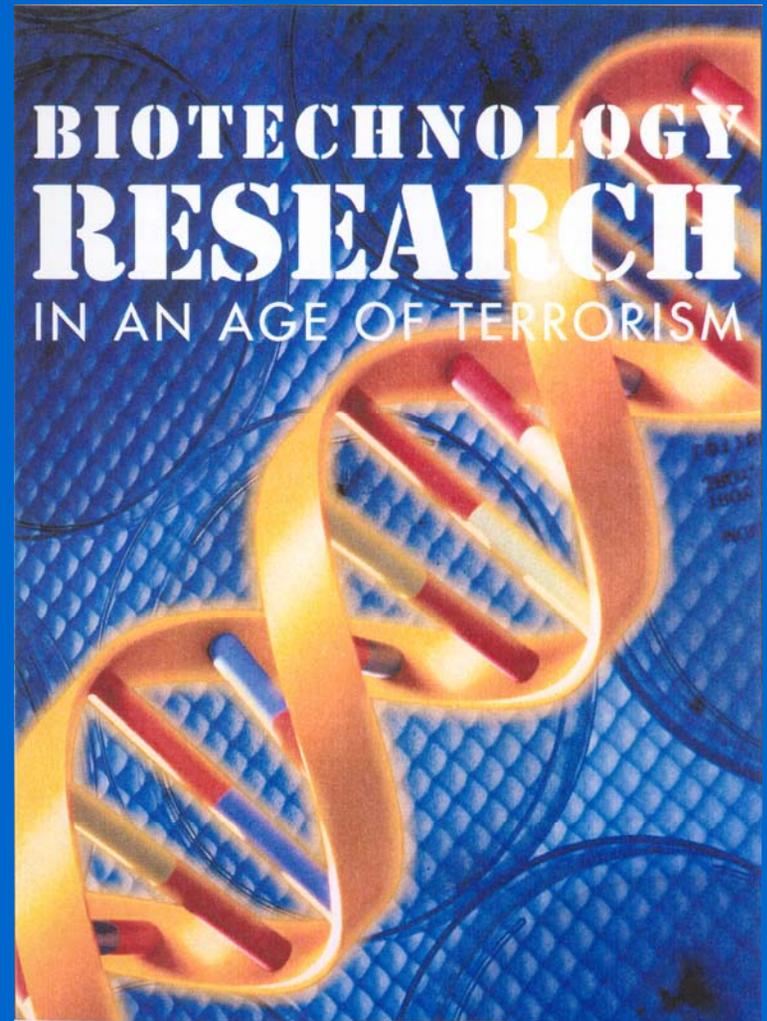


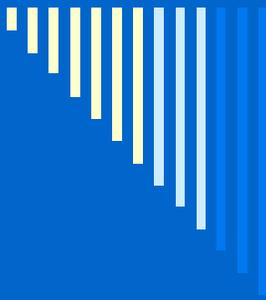
- ❑ Craig Venter made Phi-X virus in a matter of weeks from commercially available ingredients
- ❑ Virus was fully functional
- ❑ New method a step toward new lifeforms to clean up toxic waste, secrete drugs, produce fuel
- ❑ DoE funded

NRC Report on Dual Use Research

Report of the National
Research Council of the
National Academies:

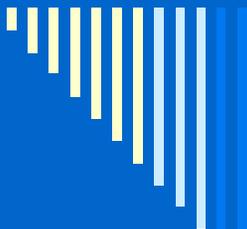
*“Biotechnology Research in an
Age of Terrorism: Confronting
the Dual Use Dilemma” (October
2003)*





Establishment of National Science Advisory Board for Biosecurity (NSABB):

- **Advisory to HHS Secretary, NIH Director, and heads of all Federal entities that conduct/support life sciences research**
- **NSABB to recommend strategies for the efficient and effective oversight of federally funded dual use life sciences research**
 - **Consider both national security concerns and needs of the life sciences research community**

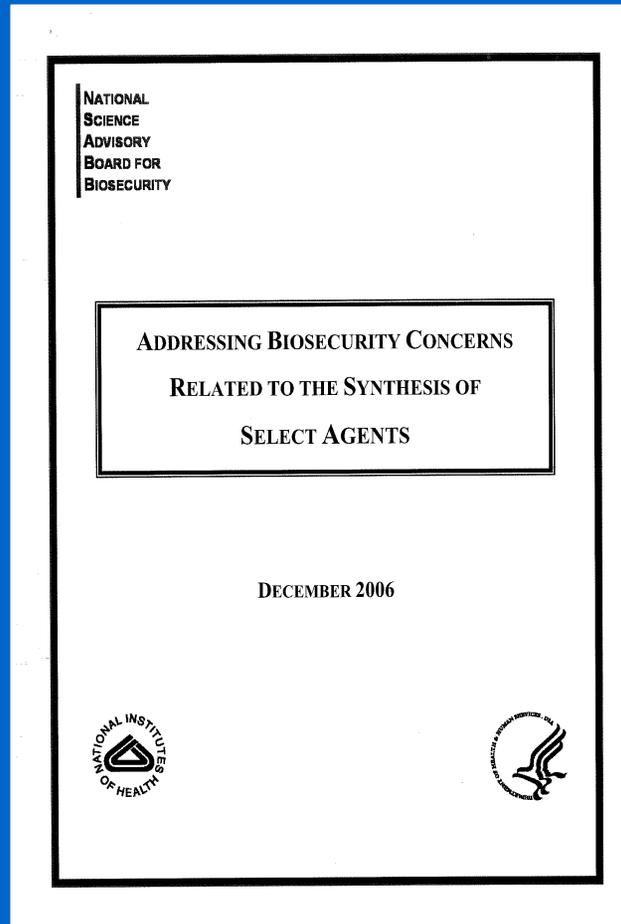


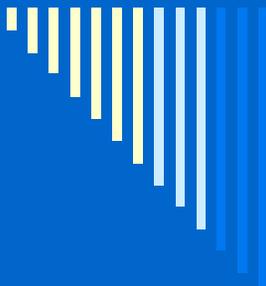
Specific Task Assigned to the NSABB: Synthetic Genomics

- 
- To identify the potential biosecurity concerns raised by synthesis of Select Agents (SA)
 - Assess the adequacy of the current regulatory and oversight framework
 - Recommend potential strategies to address any biosecurity concerns

NSABB Report

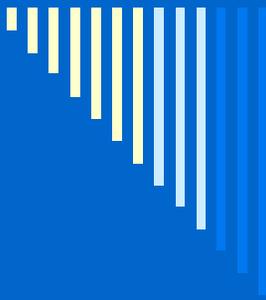
www.biosecurityboard.gov





Selected Findings and Recommendations of NSABB

- **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)
- **There is a need for biosafety principles and practices applicable to synthetic genomics**

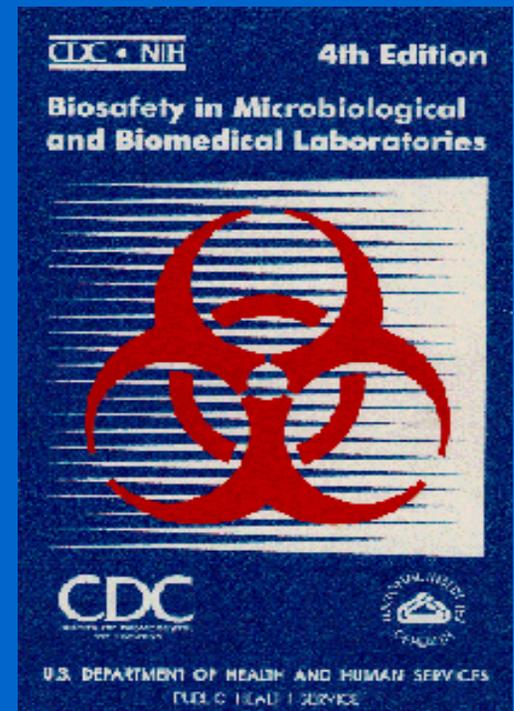


U.S. Government Policy Decisions

- HHS should update and revise as appropriate the *NIH Guidelines and Biosafety in Microbiological and Biomedical Laboratories (BMBL)*.
- Develop guidance for investigators and laboratory workers that addresses the unique safety issues related to work with certain synthetic nucleic acids and offer practical and effective options for managing risks to personnel and public health associated with such research.

Biosafety in Microbiological and Biomedical Laboratories Manual

- Agent specific, not technology driven
- References the *NIH Guidelines*



NIH Guidelines

Amendment Effective July 28, 1994, Federal Register, August 5, 1994 (59 FR 40170)
Amendment Effective April 17, 1995, Federal Register, April 27, 1995 (60 FR 20726)
Amendment Effective December 14, 1995, Federal Register, January 19, 1996 (61 FR 1482)
Amendment Effective March 1, 1996, Federal Register, March 12, 1996 (61 FR 10004)
Amendment Effective January 23, 1997, Federal Register, January 31, 1997 (62 FR 4782)
Amendment Effective September 30, 1997, Federal Register, October 14, 1997 (62 FR 53336)
Amendment Effective October 20, 1997, Federal Register, October 29, 1997 (62 FR 56126)
Amendment Effective October 22, 1997, Federal Register, October 31, 1997 (62 FR 56032)
Amendment Effective February 4, 1998, Federal Register, February 17, 1998 (63 FR 3052)
Amendment Effective April 30, 1998, Federal Register, May 11, 1998 (63 FR 20118)
Amendment Effective April 29, 1999, Federal Register, May 11, 1999 (64 FR 25561)
Amendment Effective October 2, 2000, Federal Register, October 10, 2000 (65 FR 60326)
Amendment Effective December 26, 2000, Federal Register, January 5, 2001 (66 FR 1146)
Amendment Effective December 11, 2001, Federal Register, December 11, 2001 (66 FR 64051)
Amendment Effective December 19, 2001, Federal Register, November 19, 2001 (66 FR 57970)
Amendment Effective January 10, 2002, Federal Register, December 11, 2001 (66 FR 64052)
Amendment Effective January 24, 2002, Federal Register, November 19, 2001 (66 FR 57970)

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)

April 2002

Visit the OBA Web site at:

<http://www4.od.nih.gov/oba>

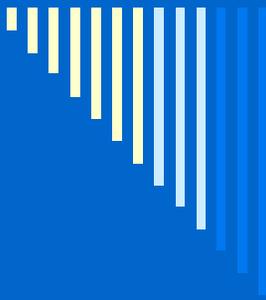
For current information on Guidelines, Protocols, Principal Investigators, Meetings,
and information about upcoming Gene Therapy Policy Conferences

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

These NIH Guidelines supersede all earlier versions and shall be effective without further notice.

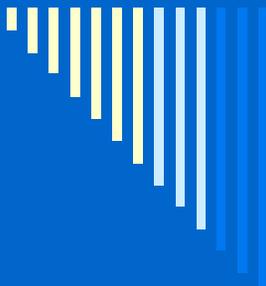
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Section I-C.	General Applicability	3
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Current Biosafety Guidance

- *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*
 - 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

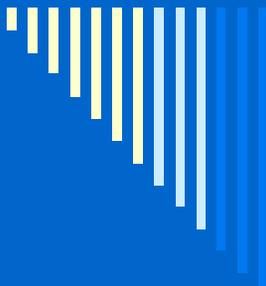


Charge to the RAC Biosafety Working Group

- Consider the application of the *NIH Guidelines* to synthetic biology
 - To what degree is this technology covered?
 - Does the scope need to be modified to capture synthetic biology?

- Develop draft recommendations regarding principles and procedures for risk assessment and management of research involving synthetic biology

- Final Proposal by end of Fiscal 2008



RAC Biosafety Working Group

RAC Biosafety Working Group Members

Stephen Dewhurst, Ph.D.

Jane Flint, Ph.D.

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Ad Hoc Experts

Drew Endy, Ph.D.

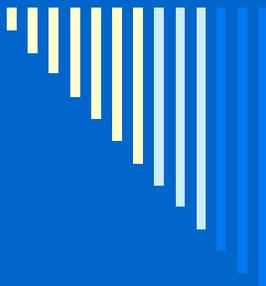
Stanley Maloy, Ph.D.

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Joseph Kozlovac, M.S., R.B.P., C.B.S.P. (USDA)



Deliberations to Date

- **Joint Meeting - RAC/NSABB:
October 11, 2007**
 - State of the Science of Synthetic Biology
 - Predicting Function from Genotype
 - Risk Assessment and Risk Management in a Context of Uncertainty

- **RAC Biosafety Working Group convened several additional times to develop draft proposal.**

Proposed Review Process

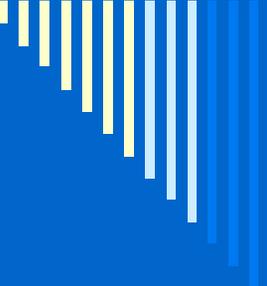


Target Date
September 2008



- ❑ Draft work products will be reviewed and approved by full RAC
- ❑ Recommendations to be published in Federal Register and opportunity for public comment and engagement
- ❑ RAC review and approval of final proposed changes
- ❑ Recommendations ultimately conveyed to NIH Director and HHS leadership

Target Date
October 2008

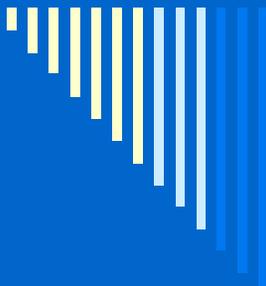


Overarching Themes

- Capture the same products made by synthetic techniques that are currently covered under scope of recombinant DNA research provided the same biosafety concerns are raised
 - **Level of review based on risk not technique**

- Develop a risk management framework that is based on the current science and what appears to be feasible in the foreseeable future

- Recognition that all future scientific developments cannot be anticipated and *NIH Guidelines* may need periodic review



Section I. Scope of the *NIH Guidelines*

Section I-A. Purpose

Current:

The purpose of the *NIH Guidelines* is to specify practices for constructing and handling:

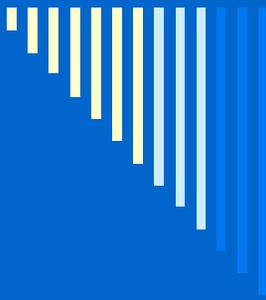
- (i) recombinant deoxyribonucleic acid (DNA) molecules, and
- (ii) organisms and viruses containing recombinant DNA molecules.

Page 8 *NIH Guidelines*

Proposed:

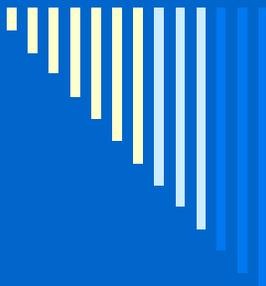
The purpose of the *NIH Guidelines* is to specify the practices for construction and manipulation of:

- (i) recombinant **nucleic acid** molecules,
- (ii) **synthesized nucleic acid molecules, including those solely or partially containing functional equivalents of nucleotides,** and
- (iii) organisms and viruses containing such molecules.



Explanation of Changes

- Clarified applicability of *NIH Guidelines* to synthetic nucleic acids (NA)
- Extended scope beyond DNA to clearly include all synthetic nucleic acids that contain functional analogs of nucleotides (e.g., those used in artificially engineered genetic systems)



Section I-B. Definition of Recombinant DNA Molecules

Current:

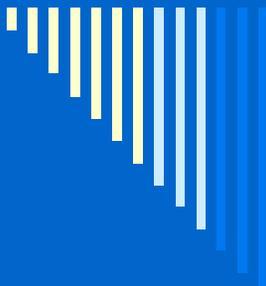
In the context of the *NIH Guidelines*, recombinant DNA molecules are defined as either:

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

Proposed:

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

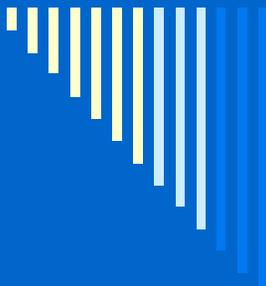
- (i) Recombinant nucleic acid molecules are molecules that are constructed by joining nucleic acid molecules and can replicate in a living cell,
- (ii) **Synthetic nucleic acids are nucleic acids that are chemically synthesized or amplified and may solely or partially contain functional equivalents of nucleotides,** and
- (iii) molecules that result from the replication of those described in (i) or (ii) above.



Explanation of Changes

- **Current definition limitations:**
 - Only explicitly mentioned DNA
 - Segments must be joined

- **Revised definition:**
 - Retained similar definition for recombinant NA
 - Added synthetic NA created without joining of segments including those that contain functional analogs of nucleotides (e.g., those used in artificially engineered genetic systems)



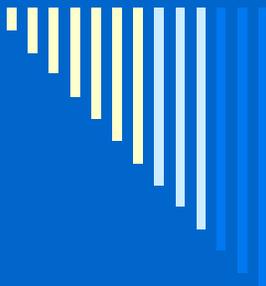
Section I-B. Definition of Recombinant DNA Molecules

Current:

•Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide (e.g. a toxin or a pharmacologically active agent) are considered as equivalent to their natural DNA counterpart. If the DNA segment is not expressed in vivo as a biologically active polynucleotide or polypeptide product it is exempt from the NIH Guidelines

Proposed:

Delete because sufficiently covered under (ii) of definition and exemptions in III-F



Section I-B. Definition of Recombinant DNA Molecules

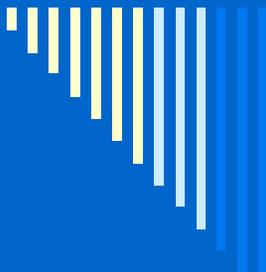
Current:

Genomic DNA of plants and bacteria that have acquired a transposable element, even if the latter was donated from a recombinant vector no longer present, are not subject to the NIH Guidelines unless the transposon itself contains recombinant DNA

Proposed:

New section III-F-7

Those that consist in part of a transposable element, as long as the transposable element does not contain recombinant or synthetic DNA. These molecules are exempt even if they originate from a recombinant or synthetic vector, as long as the vector is no longer present.



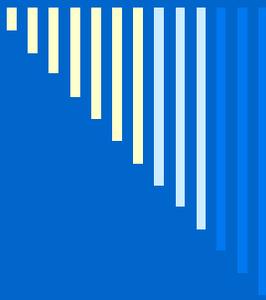
Section III-F. Exempt Experiments

Current:

The following recombinant DNA molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee is not required:

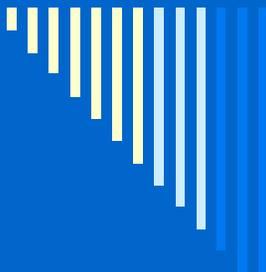
Proposed:

The following recombinant and/or synthetic nucleic acids molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee. **However, other standards of biosafety may still apply to such research (for example, the BMBL, DOD or OSHA standards):**



Explanation of Changes

- Added language to emphasize that research exempt from *NIH Guidelines* will still have biosafety considerations and that other standards may be applicable



Section III-F: Exempt Experiments

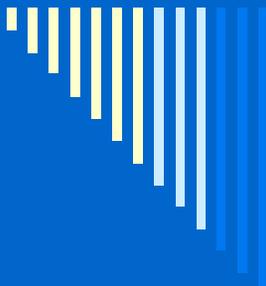
Current:

Section III-F-1.

Insert new exemption and renumber current exemptions

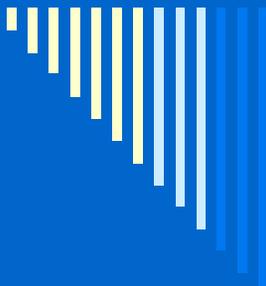
Proposed:

Section III-F-1. Synthetic nucleic acids that can not replicate, and that are not deliberately transferred into one or more human research participants (see Section III-C and Appendix M).



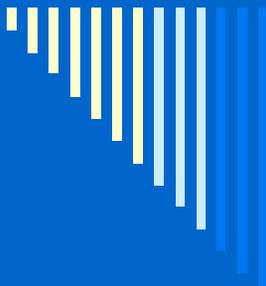
Explanation of Changes

- **Consistent with IBC overview of laboratory rDNA research that is limited to molecules that can replicate or are derived from such molecules.**
- **Consistent with current Appendix M (Human Gene Transfer) that covers use of non-replicating molecules derived through recombinant technology that has steps involving replication (e.g., replication incompetent vectors, RNAi, antisense RNA, etc.).**
- **Exemption applies to laboratory research but not human gene transfer. This distinction is based on the difference in risk likely between inadvertent lab exposure and deliberate, clinical gene transfer.**



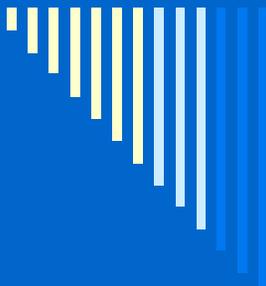
Synthetic NA and Human Gene Transfer

- Gene transfer trials raise unique safety and ethical issues because the intent is to alter the genetic mechanisms of the cell and direct a phenotypic change that has a clinical impact.
- Currently, most gene transfer vectors as administered should not replicate, therefore review of human gene transfer is not based on the replicating nature of the vector.
- Off-target effects of the NA including the risk of insertional mutagenesis and other unintended effects, e.g., unanticipated immunological responses, may be unique to human gene transfer.
- The constitutive expression of the gene may lead to persistence of transgene product that does not have a predictable “half-life.”
- The doses used in human gene transfer likely increases these risks
- Public trust will be enhanced by continuing open review of human trials that involve even transient alterations of genomic information with the intent of altering phenotype.



Questions to be Considered for Laboratory Work

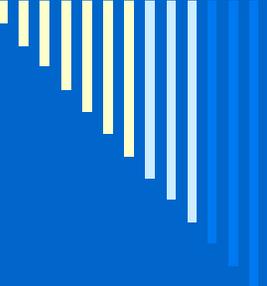
- Is there a sufficient distinction between the risks of research with replicating vs. non-replicating synthetic agents to warrant the exemption?
 - What are the risks with use of replication incompetent integrating vectors in the laboratory? For examples, preclinical research with recombinant lentiviral vectors is covered because the vectors are generated using a step involving replication. At the lower doses typically used in laboratory experiments, are the risks to the laboratory worker of such non-replicating, synthetic NA research sufficiently low to exempt from the *NIH Guidelines*?



Questions to be Considered for Laboratory Work

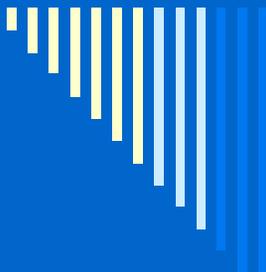
- The increased risk for human gene transfer is in part related to dose used in human gene transfer
 - Should this exemption be limited to experiments with low concentrations of nucleic acids?

- Are there examples of non-replicating, synthetic NA research that should not be exempt due to greater potential risks?



Questions to be Considered for Human Gene Transfer

- Are there classes of non-replicating molecules used in human gene transfer which should be exempt due to lower potential risks (e.g., antisense RNA, ribozymes, RNAi etc.)?
 - If so, what criteria should be applied to determine which classes?



Section III-F. Exempt Experiments

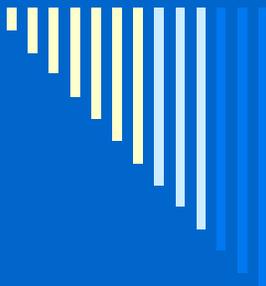
Current:

Section III-F-1. Those that are not in organisms or viruses.

Page 20 *NIH Guidelines*

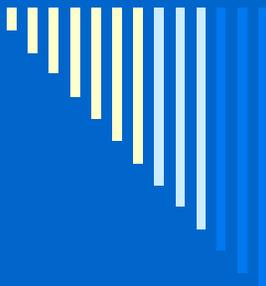
Proposed:

Section III-F-2. Recombinant or **synthetic nucleic acids** 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 (see Section III-F-8).**



Questions to be Considered

- **Exception added so that research involving replicating NA placed in cells or modified to enable penetration through cell membranes would not be exempt because such preparations may have increased risk in the laboratory.**



Section III-F. Exempt Experiments

Current:

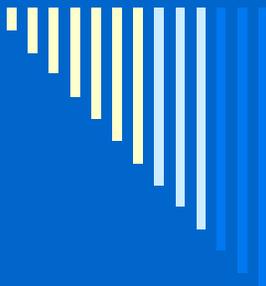
Section III-F-2.

Those that consist entirely of DNA segments from a single nonchromosomal or viral DNA source, though one or more of the segments may be a synthetic equivalent.

Proposed:

Section III-F-3.

Recombinant or synthetic nucleic acids that consist solely of the **exact nucleic acid sequence from a single source that exists contemporaneously in nature.**

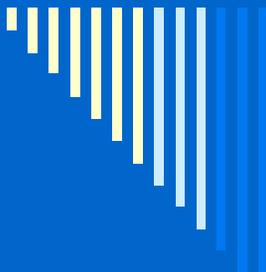


Explanation of Changes

- Under the current language, molecules from a single source but containing duplications or deletions are exempt. However, such agents may have different risks than the wild type parent.
- Revised language is intended to clarify that exempt molecules must have the exact sequence from a functional wild type agent currently existing in nature (e.g., reconstructing 1918 influenza virus would not be exempt research)

Question:

- Should we maintain the specificity that “single source” refers to single chromosomal, non-chromosomal or viral source?
- How should agents nearing eradication (e.g., polio) be treated? Are there restrictions on such wild type agents that might be applicable to synthetic agents?



Section III-E-1. Experiments Involving the Formation of rDNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus

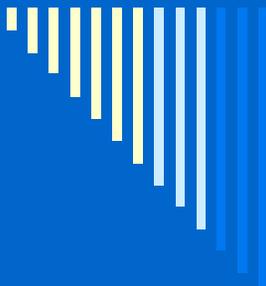
(IBC registration simultaneous with initiation)

Current:

Recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family being considered identical [see [Section V-J](#), *Footnotes and References of Sections I-IV*]) may be propagated and maintained in cells in tissue culture using BL1 containment. For such experiments, it must be demonstrated that the cells lack helper virus for the specific Families of defective viruses being used. If helper virus is present, procedures specified under [Section III-D-3](#), should be used. The DNA may contain fragments of the genome of viruses from more than one Family but each fragment shall be less than two-thirds of a genome.

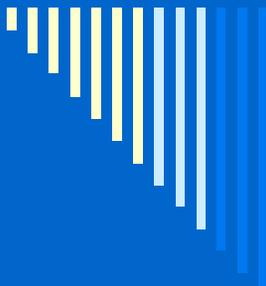
Proposed:

Recombinant and synthetic NA molecules containing no more than **half** of the genome of any **one risk group 3 or 4** eukaryotic virus (all viruses from a single Family being considered identical [see [Section V-J](#), *Footnotes and References of Sections I-IV*]) may be propagated and maintained in cells in tissue culture using BL-1 containment (as defined in Appendix G) provided **there is evidence that the resulting NA molecules in these cells are not capable of producing a replication competent virus**. For such experiments, it must **also** be demonstrated that the cells lack helper virus for the specific Families of defective viruses being used. If helper virus is present, procedures specified under [Section III-D-3](#), should be used.



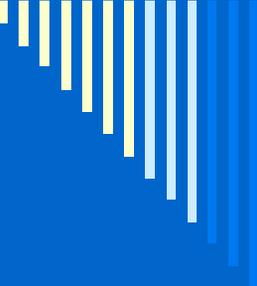
Explanation of Changes

- Concerns were raised that the section may not adequately apply to potential synthetic biology agents derived from multiple sources of NA or even to some wild type viruses (e.g., HSV) which may function with less than 2/3 genome present
- Half of the genome was chosen to be consistent with more recent reports of the biology of certain viruses
- The use of BL1 containment was clarified to be appropriate only after demonstration that the preparation(s) are free of replication competent virus which may be generated by homologous recombination with endogenous proviruses or the presence of helper virus.



Explanation of Changes

- **Also consistent with Appendix C-I: Recombinant DNA in Tissue Culture**
 - **Recombinant DNA molecules containing less than one-half of any eukaryotic viral genome..., that are propagated and maintained in cells in tissue culture are exempt from these *NIH Guidelines* with the exceptions listed in Appendix C-I-A.**
 - **Per Appendix C-1-A, this exemption only applies to RG 1 and 2 organisms and not to experiments involving DNA from Risk Groups 3, 4, or restricted organism.**



Section IV-A. Policy

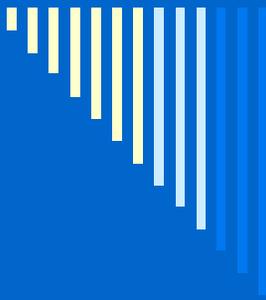
Current:

Section IV-A. Policy

The *NIH Guidelines* will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, *it is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to their specifics.*

Proposed:

The NIH Guidelines will never be complete or final since all experiments involving recombinant and/or synthetic nucleic acids cannot be foreseen. **The utilization of new genetic manipulation techniques may enable work previously done by recombinant means to be accomplished faster, more efficiently or at larger scale.** These techniques have not as yet yielded organisms that present safety concerns that fall outside the current RA framework used for rDNA research. **Nonetheless, an appropriate risk-assessment of experiments involving these techniques must be conducted taking into account the way these approaches may alter the risk assessment. In addition, as the field develops, new techniques and applications need to be monitored and assessed to see if a new oversight framework may be needed. As new techniques develop, the *NIH Guidelines* should be periodically reviewed to determine whether and how such research should be explicitly addressed.** *Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to their specifics...*



Explanation of Changes

- Emphasizes that the *NIH Guidelines* are an evolving document which may be modified to address new developments in research or techniques.

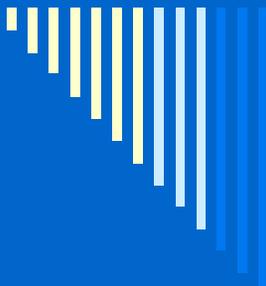


Section II. Safety Considerations

Current: Section II-A-3. Comprehensive Risk Assessment

In deciding on the appropriate containment for an experiment, the initial risk assessment from [Appendix B](#), *Classification of Human Etiologic Agents on the Basis of Hazard*, should be followed by a thorough consideration of the agent itself and how it is to be manipulated. Factors to be considered in determining the level of containment include agent factors such as: virulence, pathogenicity, infectious dose, environmental stability, route of spread, communicability, operations, quantity, availability of vaccine or treatment, and gene product effects such as toxicity, physiological activity, and allergenicity. Any strain that is known to be more hazardous than the parent (wild-type) strain should be considered for handling at a higher containment level. Certain attenuated strains or strains that have been demonstrated to have irreversibly lost known virulence factors may qualify for a reduction of the containment level compared to the Risk Group assigned to the parent strain (see [Section V-B](#), *Footnotes and References of Sections I-IV*).

A final assessment of risk based on these considerations is then used to set the appropriate containment conditions for the experiment (see [Section II-B](#), *Containment*). The containment level required may be equivalent to the Risk Group classification of the agent or it may be raised or lowered as a result of the above considerations...

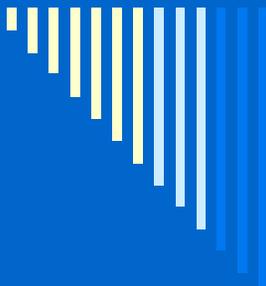


Section II. Safety Considerations

Proposed: Section II-A-3. Comprehensive Risk Assessment

Insert between paragraphs on previous slide:

While the initial RA is based on the identification of the RG of the parent agent, as technology moves forward, it may be possible to develop a chimera in which the parent agent may not be obvious. In such cases, the risk assessment should involve at least two levels of analysis. The first involving a consideration of the RGs of the source(s) of the sequences and the second an analysis of the functional attributes of these sequences (e.g., sequence associated with virulence factors, transmissibility, etc.). It may be prudent to first consider the highest RG classification of any agent sequence included in the chimera. Other factors to be considered include the percentage of the genome contributed by each of multiple parent agents, and the predicted function or intended purpose of each contributing sequence. The initial assumption should be that such sequence will function as predicted in the original host context.

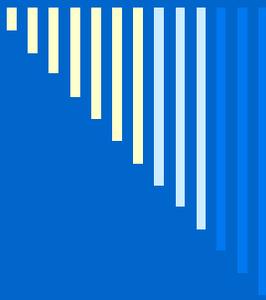


Section II. Safety Considerations

Proposed: Section II-A-3. Comprehensive Risk Assessment

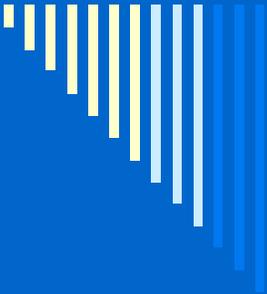
(Continued)

The IBC must also be cognizant that the introduction of the combination of certain sequences may result in a new organism whose risk profile could be higher than that of the contributing organisms or sequences. The synergistic function of these sequences may be one of the key attributes to consider in deciding whether a higher containment level is warranted. A new risk may occur with a chimera formed through combination of sequences from a number of organisms or combining of transgenes that direct the acquisition of a new phenotype.



Explanation of Changes

- Provides additional guidance for evaluating research utilizing the capabilities of synthetic biology that may raise more complex issues for risk assessment:
 - More difficult identification of a parent agent due to multiple potential parent sources or novel sequence
 - Synergistic effects from combining sequences from different sources in a novel context
 - Need to predict function of sequence(s)



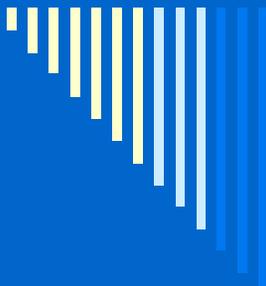
Major Actions under Section III-A-1-a

Current:

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.

Proposed:

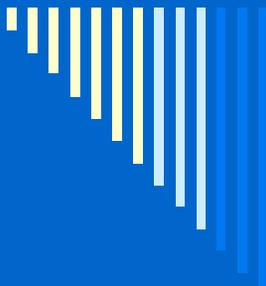
The deliberate transfer of a drug resistance trait to microorganisms, if such acquisition could compromise the ability to treat or manage disease agents in human and veterinary medicine, or agriculture will be reviewed by RAC (see Section V-B, *Footnotes and References of Sections I-IV*)



Major Actions under Section III-A-1-a

Additional Proposed Language:

- If there are one or more alternative drugs, one must consider whether removal of a one of these alternative drugs could compromise the ability to control infection in certain groups or subgroups; i.e. putting them at risk of developing an infection by such microorganism for which alternative treatments may not be available. Examples of potentially affected groups or subgroups include, but are not limited to: persons who are allergic to effective alternative treatments, immunocompromised individuals, pregnant women, pediatric populations, and individuals in countries where the alternative effective treatment is not readily available



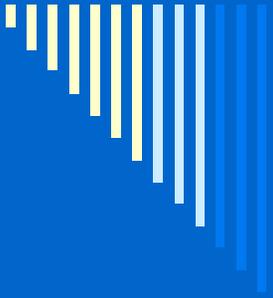
Explanation of Changes

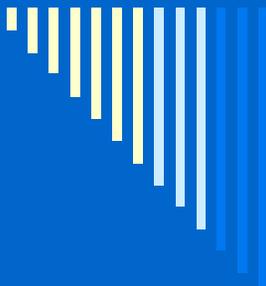
- Deleted “**that are not known to acquire the trait naturally**” because of uncertain clinical relevance:
 - All forms of antibiotic resistance occur naturally
 - Use of antibiotics created a selective pressure for the resistant strains

- Recognition that even if there is a some level of resistance to that drug, that drug may still be useful in control of the disease.

- Clarified that removal of a drug that is not considered the “drug of choice” can still raise important clinical and public health considerations for certain subpopulations

- Additional changes will be made to other portions of the *NIH Guidelines* so that NIH OBA will have the discretion to review and approve certain experiments that have been previously reviewed by the RAC and approved by the NIH Director as a Major Action.





Section III-B. Experiments that Require NIH/OBA and IBC Approval before Initiation

Section III-B-2 Experiments that have been approved (under Section III-A-1-a) as Major Actions under the *NIH Guidelines*

- **Certain experiments that have been reviewed by the RAC and approved by the NIH Director as a Major Action may be eligible for approval by NIH/OBA and the Institutional Biosafety Committee before initiation. These experiments will be reviewed by NIH/OBA following submission of relevant information.**
- **At NIH/OBA's discretion, these experiments may not be eligible for review and approval under this section and will require approval as Major Actions under Section III-A-1-a of the *NIH Guidelines*.**