

Introduction to the Proposed Revisions to the NIH Guidelines for Research Involving Recombinant DNA

Biosafety and the Emerging Technology of
Synthetic Biology

Stephen Dewhurst, Ph.D.

June 23, 2009



Synthetic Nucleic Acids and the *NIH Guidelines*

□ OVERVIEW

- Why were these changes undertaken and how were they developed?
- Proposed Amendments to the *NIH Guidelines* Regarding Synthetic Nucleic Acids
 - Basic and Clinical research with synthetic nucleic acid molecules
- Discussion Questions: Sessions I and II

National Science Advisory Board for Biosecurity Report

NATIONAL
SCIENCE
ADVISORY
BOARD FOR
BIOSECURITY

ADDRESSING BIOSECURITY CONCERNS
RELATED TO THE SYNTHESIS OF
SELECT AGENTS

DECEMBER 2006



NSSAB Finding on Synthetic Genomics and Biosafety

- ❑ 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.**

Current Biosafety Guidance

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

Recombinant DNA:

- 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

Current Biosafety Guidance

- ❑ ***NIH Guidelines* are limited to synthetic DNA joined by recombinant methods**
 - Does not cover synthetic DNA that is synthesized *de novo*
 - Does not cover synthesized RNA viruses

- ❑ **Biosafety in Microbiological and Biomedical Laboratories Manual (BMBL)**
 - Agent specific, not technology driven
 - References *NIH Guidelines* with respect to synthetic recombinant molecules

Implementation of Recommendation by U.S. Government (USG)

- ❑ NSABB recommendations were considered through a trans-federal policy coordination process
 - Led by the White House Homeland Security Council and Office of Science and Technology Policy
- ❑ Recommendation on need for biosafety guidance accepted by USG with understanding that implementation would be through modification of *NIH Guidelines* as appropriate

Charge to the Recombinant DNA Advisory Committee

- ❑ 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 research?

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

Review Process

- ❑ Initial proposal developed by a sub-group of the RAC, the Biosafety Working Group
- ❑ Proposed revisions reviewed and approved by the full RAC committee in March 2008
- ❑ Proposal published in Federal Register in March 2009 with opportunity for public comment

RAC Biosafety Working Group Roster

March 2008

Stephen Dewhurst, Ph.D.

Howard Federoff, M.D., Ph.D.

Jane Flint, Ph.D.

Joseph Kanabrocki, Ph.D., C.B.S.P.

Louis Kirchhoff, M.D., M.P.H.

Claudia Mickelson, Ph.D.

Nicholas Muzyczka, Ph.D.

Naomi Rosenberg, Ph.D.

Robyn Shapiro, J.D.

Nikunj Somia, Ph.D.

***Ad Hoc* Members**

Drew Endy, Ph.D.

Stanley Maloy, Ph.D.

Ronald Weiss, Ph.D.

Agency Representatives

J. Michael Miller, Ph.D. (CDC)

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

Overarching Themes

- ❑ Capture the same products made by synthetic techniques that are currently covered under the *NIH Guidelines* for 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

- ❑ Recognize that not all future scientific developments can be anticipated, so that the *NIH Guidelines* will need periodic review and updating

Section I-B. Proposed Definition of Recombinant DNA Molecules

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 that may wholly or partially contain functional equivalents of nucleotides, or**
- (iii) molecules that result from the replication of those described in (i) or (ii) above.

Basic, Non-Clinical Research with Non-Replicating Synthetic Nucleic Acids

- A new section of the *NIH Guidelines* exempts synthetic nucleic acids that cannot replicate provided these are not used in human gene transfer
 - Exemption of non-replicating nucleic acids (NA) is consistent with current *NIH Guidelines* for laboratory rDNA research
 - Limited to molecules that can replicate or are derived from such molecules.
 - Exemption will not apply to non-replicating synthetic NA used in human gene transfer.
 - Difference based on potential for increased risk from deliberate administration to a human in a clinical trial compared to inadvertent lab exposure

Risk of Non-Replicating Synthetic NAs: Basic Research

- Exposure in the lab to a low dose of non-replicating synthetic nucleic acid sequence is considered low risk
 - Low risk because this type of NA inside a cell cannot replicate and spread
 - Could not spread in the environment if a breach occurred
 - Risk is similar to that of a chemical exposure although nucleic acids are not toxic in and of themselves

Risks in Human Gene Transfer

- ❑ Doses used in human gene transfer trials are deliberately high compared to what may be expected by an inadvertent lab exposure
- ❑ Many human gene transfer trials use replication incompetent vectors however known safety risks are due to transgene effects, insertional mutagenesis, and immunological responses - these are independent of vector replication
- ❑ Human gene transfer raises unique scientific, medical and ethical issues that warrant special oversight

RISK ASSESSMENT UNDER THE *NIH GUIDELINES*

**DOES THE SAME FRAMEWORK APPLY
FOR SYNTHETIC NA?**

Risk Groups (RG) Under the *NIH Guidelines*

- **RG1** Agents that are not associated with disease in healthy adult humans
- **RG2** Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available
- **RG3** 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)
- **RG4** Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *are not usually* available (high individual risk and high community risk)

Containment Level (Biosafety Level) may be raised or lowered depending on a comprehensive risk assessment.

Risk Assessment under the *NIH Guidelines*

- ❑ Starting point for the Risk Assessment (RA) is the non-recombinant “parent” organism
- ❑ Containment may be raised or lowered depending upon the recombinant agent factors and manipulation:
 - Virulence
 - Pathogenicity
 - Infectious Dose
 - Environmental stability
 - Route of Spread
 - Communicability
 - Operations
 - Quantity
 - Availability of vaccine or treatment
 - Gene product effects:
 - Toxicity
 - Physiologic activity
 - Allergenicity

Risk Assessment under the *NIH Guidelines*

□ Biological Containment

- Experiments with rDNA lend themselves to a third containment mechanism – biological barriers that limit either:
 - Infectivity of a vector or vehicle (plasmid or virus) for specific hosts, or
 - Its dissemination and ability to persist in the environment

Risk Assessment (RA) for Synthetic NAs

- **RA is not fundamentally different; however**
 - As the technology moves forward, chimeras may be generated for which the parent organism is not obvious
 - RA should consider the organism(s) from which the sequences were derived and the function of those sequences
 - It may be prudent to first consider the highest risk group classification of any agent sequence in the chimera

Summary of Proposed Revisions

- ❑ Research with synthetic NAs in most cases present biosafety risks that are comparable to rDNA research
- ❑ Certain work with non-replicating synthetic NAs may not require oversight under the *NIH Guidelines* although other biosafety standards will apply
- ❑ The current RA framework can be used with attention to the unique aspects of this technology

Goals for Meeting

- **Session I:** Review of Biosafety Considerations for Basic, Non-Clinical Research with Synthetic Nucleic Acids
 - Is the exemption for non-replicating synthetic nucleic acids appropriate from a biosafety perspective
- **Session II:** Human Gene Transfer with Non-Replicating Synthetic Nucleic Acids
 - Are the risks sufficiently understood to distinguish non-replicating synthetic nucleic acids from vector-mediated gene transfer?

Goals for Meeting

- ❑ **Session III:** Review of Proposed Language for Section III-A-1: Introduction of Drug Resistance into microorganisms
 - Should the criterion for “known to acquire the trait naturally” be retained?
- ❑ **Session IV:** Experiments With rDNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus: Section III-E-1
 - Review of rationale for change and public comments

