NIH Guidelines for Research Involving Recombinant DNA

Biosafety and Synthetic Nucleic Acids

Jacqueline Corrigan-Curay, J.D., M.D.

October 19, 2010

Impetus for Review and Revisions

- **The U.S. Government should examine the language and implementation of current biosafety guidelines 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 covered by the guidelines.**

NSABB Report: *Addressing Biosecurity Concerns Related to the Synthesis of Select Agents (2007)*

Biosafety and Synthetic Nucleic Acids

- **NIH Tasked with Review of the *NIH Guidelines for Research Involving Recombinant DNA* to determine the need to revise the Guidelines to address research with synthetic nucleic acids.**

- **NIH consulted with the NIH Recombinant DNA Advisory Committee (RAC).**

Definition of Recombinant DNA

- Current *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

Section I-B. Revised Proposed Definition

In the context of the *NIH Guidelines*, recombinant and synthetic nucleic acids are defined as either:
(i)molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell, i.e. recombinant nucleic acids,
(ii)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.

Basic Research with Synthetic Nucleic Acids that cannot Replicate

- **New proposed Section F-1 will exempt the following from the NIH Guidelines:**
  - **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, and

    (4) are not considered human gene transfer under Section III-C.

Clinical Research with Synthetic Nucleic Acids that cannot Replicate

Proposed Section III-C-1: Human gene transfer is the deliberate transfer into human research participants of either:

- Recombinant DNA molecules, or DNA or RNA derived from recombinant DNA molecules, or
- Synthetic DNA or RNA that meet any one of the following criteria:
  - Contains more than 100 nucleotides; or
  - Possesses 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.

Revised Risk Assessment for Synthetic Nucleic Acids

- As technology moves forward, it may be possible to develop organisms containing genetic sequences from multiple sources such that the parent organism may not be obvious
- In such cases, the risk assessment should take into consideration:
  - The risk groups of the organisms from which these sequences are derived
  - The function of these sequences in their original host context

Current Status

- RAC approved final recommendations at June 16-17, 2010 meeting
- Draft Federal Register notice undergoing review