DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel; Urothelium and UTI Program Projects.

Date: March 27, 2009.

Time: 8:30 a.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Bethesda Marriott Suites, 6711 Democracy Boulevard, Bethesda, MD 20817.

Contact Person: Lakshmanan Sankaran, PhD, Scientific Review Officer, Review Branch, DEA, NIDDK, National Institutes of Health, Room 755, 6707 Democracy Boulevard, Bethesda, MD 20892–5452, (301) 594–7799, *ls38z@nih.gov.*

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel; Methotrexate Response In Treatment of UC.

Date: April 1, 2009.

Time: 3 p.m. to 4:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Two Democracy Plaza, 6707 Democracy Boulevard, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Paul A. Rushing, PhD, Scientific Review Officer, Review Branch, DEA, NIDDK, National Institutes of Health, Room 747, 6707 Democracy Boulevard, Bethesda, MD 20892–5452, (301) 594–8895, *rushingp@extra.niddk.nih.gov.*

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel; Lifestyle Intervention to Treat Erectile Dysfunction (LITE).

Date: April 2, 2009.

Time: 11 a.m. to 12:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Two Democracy Plaza, 6707 Democracy Boulevard, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Paul A. Rushing, PhD, Scientific Review Officer, Review Branch, DEA, NIDDK, National Institutes of Health, Room 747, 6707 Democracy Boulevard, Bethesda, MD 20892–5452, (301) 594–8895, *rushingp@extra.niddk.nih.gov.*

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel; Immunosuppression Withdrawal for Stable Pediatric Liver Transplant Recipients.

Date: April 2, 2009.

Time: 3 p.m. to 4:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Two Democracy Plaza, 6707 Democracy Boulevard, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Paul A. Rushing, PhD, Scientific Review Officer, Review Branch, DEA, NIDDK, National Institutes of Health, Room 747, 6707 Democracy Boulevard, Bethesda, MD 20892–5452, (301) 594–8895, *rushingp@extra.niddk.nih.gov.*

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel; Ancillary Studies to Ongoing NIDDK Clinical Research Studies.

Date: April 3, 2009.

Time: 1 p.m. to 2 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Two Democracy Plaza, 6707 Democracy Boulevard, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Barbara A Woynarowska, PhD, Scientific Review Officer, Review Branch, DEA, NIDDK, National Institutes of Health, Room 754, 6707 Democracy Boulevard, Bethesda, MD 20892–5452, (301) 402–7172, *woynarowskab@niddk.nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.847, Diabetes, Endocrinology and Metabolic Research; 93.848, Digestive Diseases and Nutrition Research; 93.849, Kidney Diseases, Urology and Hematology Research, National Institutes of Health, HHS)

Dated: February 26, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–4629 Filed 3–3–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Mental Health; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Mental Health Special Emphasis Panel; Center for AIDS Intervention Research Core Support.

Date: March 27, 2009.

Time: 11 a.m. to 2 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, Neuroscience Center, 6001 Executive Boulevard, Rockville, MD 20852, (Telephone Conference Call).

Contact Person: Enid Light, PhD, Scientific Review Officer, Division of Extramural Activities, National Institute of Mental Health, NIH, Neuroscience Center, 6001 Executive Boulevard, Room 6132, MSC 9608, Bethesda, MD 20852–9608, 301–443–0322, *elight@mail.nih.gov.*

(Catalogue of Federal Domestic Assistance Program Nos. 93.242, Mental Health Research Grants; 93.281, Scientist Development Award, Scientist Development Award for Clinicians, and Research Scientist Award; 93.282, Mental Health National Research Service Awards for Research Training, National Institutes of Health, HHS)

Dated: February 26, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–4630 Filed 3–3–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of consideration of a proposed action under the *NIH Guidelines.*

SUMMARY: In 2006, the National Science Advisory Board for Biosecurity, an advisory committee to the Secretary of the Department of Health and Human Services, the NIH Director and all Federal entities that conduct/support life sciences research published a report

entitled ''Addressing Biosecurity Concerns Related to the Synthesis of Select Agents.'' [1] The report included a recommendation that the United States Government (USG) ''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 addressed by the guidelines.'' The USG adopted this recommendation and asked NIH to review the *NIH Guidelines for Research with Recombinant DNA (NIH Guidelines)* to evaluate whether these guidelines need to be revised to address biosafety concerns for research with synthetic DNA. With the advice of the NIH Recombinant DNA Advisory Committee (RAC), which is responsible for advising the NIH Director on all aspects of recombinant DNA technology, including revisions to the *NIH Guidelines,* the following proposed changes were developed. As outlined in more detail below, the proposed changes will expand the scope of the *NIH Guidelines* to specifically cover nucleic acid molecules made solely by synthetic means. The changes apply to basic laboratory research and clinical research. In addition, changes were made to clarify the criteria for determining whether an experiment to introduce drug resistance into a microorganism raises important public health issues such that it must be reviewed by the RAC and approved by the NIH Director. Finally, the proposed amendments speak to the appropriate level of review for recombinant or synthetic experiments involving more than half but less than two-thirds of the genome of certain viruses in tissue culture. These changes were prompted by an increased understanding of the biology of certain viruses that demonstrate there may be biosafety risks with certain viruses that contain less than two-thirds of the viral genome.

DATES: The public is encouraged to submit written comments on this proposed action. Comments may be submitted to OBA in paper or electronic form at the OBA mailing, fax, and e-mail addresses shown below under the heading **FOR FURTHER INFORMATION CONTACT**. All comments should be submitted by May 4, 2009. All written comments received in response to this notice will be available for public inspection in the NIH OBA office, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892–7985, weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional information about these proposed changes, please contact OBA by e-mail at *oba@od.nih.gov,* or telephone at 301–496–9838. Comments can be submitted to the same e-mail address or by fax to 301–496–9839 or mail to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, Maryland 20892–7985. Background information may be obtained by contacting NIH OBA by e-mail at *oba@od.nih.gov.*

SUPPLEMENTARY INFORMATION:

Background: Nucleic Acid (NA) synthesis technology, in combination with other rapidly evolving capabilities in the life sciences, such as directed molecular evolution and viral reverse genetics, has galvanized segments of the scientific community. It also has captured the attention of the general public and policymakers, prompting far-reaching questions about the potential use of these techniques—including the synthesis of novel forms of life. These techniques promise to accelerate scientific discovery and have the potential to yield new therapeutics for disease. This same technology may lead to the modification of existing or the creation of new pathogens with unexpected and potentially dangerous characteristics.

In 2004, the National Research Council (NRC) published a report that made an important contribution to the development of biosecurity policy for the biological sciences, ''Biotechnology in the Age of Terrorism: Confronting the Dual Use Issue.'' [2] While this report was not the first to recognize this problem, and indeed the U.S. Government (USG) had already initiated an examination of security issues in the biological sciences, the NRC report laid out a series of actions to improve biosecurity in life science research, one of which was the creation of an advisory body. The USG recognized the need for such an advisory body and formed the National Science Advisory Board for Biosecurity (NSABB) to advise the U.S. Government on strategies for minimizing the potential for misuse of information and technologies from life sciences research, taking into consideration both national security concerns and the needs of the research community. The NSABB, as it is chartered, differs somewhat from the panel proposed by the NRC report, but has aims similar to those envisioned by the NRC committee.

At the NSABB's first meeting, the Secretary of Health and Human Services tasked the NSABB with identifying potential biosecurity concerns raised by the rapidly advancing ability to synthesize select agents (7 CFR part 331, 9 CFR part 121, and 42 CFR part 73) and other dangerous pathogens. In 2006, NSABB published a report entitled ''Addressing Biosecurity Concerns Related to the Synthesis of Select Agents.'' [3] In that report the NSABB noted that practitioners of synthetic genomics or researchers using synthetic nucleic acids in the emerging field of synthetic biology are often educated in disciplines that do not routinely include formal training in biosafety, *e.g.*, engineering. These researchers may be uncertain about when to consult an Institutional Biosafety Committee (IBC).

The NSABB recommended to the Secretary of the Department of Health and Human Services that the language and implementation of current biosafety guidelines be examined to ensure that such guidelines and regulation provide adequate guidance for working with synthetically derived nucleic acids. This recommendation on the need for biosafety guidance was considered by the Executive Branch through a trans-Federal policy coordination process. The recommendation on the need for biosafety guidance was accepted by the U.S. Government with the understanding that implementation would be through modification of the *NIH Guidelines* as appropriate. The changes to the *NIH Guidelines* would then be cross-referenced in the Centers for Disease Control and Prevention/NIH publication entitled: *Biosafety in Microbiological and Biomedical Laboratories* (BMBL).

The Recombinant DNA Advisory Committee (RAC) considered the applicability of the *NIH Guidelines* to the creation of, and experiments with synthetic nucleic acids (''synthetic biology'') and whether the *NIH Guidelines* adequately address the biosafety concerns that may arise from this research. The proposed revisions to the *NIH Guidelines* are intended to clarify the applicability of the *NIH Guidelines* to research with synthetic nucleic acids and provide principles and procedures for risk assessment and management of such research.

While the initial NSABB recommendation focused on synthetic

[1] The full document is available at *http://oba.od.nih.gov/biosecurity/pdf/Final_NSABB_Report_on_Synthetic_Genomics.pdf.*

[2] The report is available from the National Academies Press: *http://www.nap.edu/catalog.php?record_id=10827#toc.*

[3] The full document is available at *http://oba.od.nih.gov/biosecurity/pdf/Final_NSABB_Report_on_Synthetic_Genomics.pdf.*

genomics, which is the synthesis of nucleic acids using chemical or other methods that do not require traditional recombinant DNA techniques, it was recognized that this may be only be the first step in a research proposal. The synthetic nucleic acid will then likely be placed in cells or organisms. As it is articulated in the *NIH Guidelines,* it is the manipulation of the recombinant nucleic acids that leads to different biosafety concerns. As such, the focus of any review of synthetic genomics from a biosafety perspective needs to address the biological experiments that will be carried out. Therefore, with respect to the NIH Guidelines, the task was to review the biosafety considerations of introducing these synthetic nucleic acids into biological systems.

Synthetic genomics utilizes different techniques than traditional recombinant methods of synthesis; however, the ultimate product may be the same. The biosafety considerations in most cases are related to the product being produced more than the technique used. In other words, the technique for creating sequences of nucleic acids is not determinative of virulence, transmissibility and pathogenicity of the product, which are key considerations in biosafety. There is no one to one correlation between increasing nucleic acid diversity and increasing risk of harm. Indeed, what has developed in nature involves complex and highly regulated sequences of nucleic acids in which there is often synergy between genes. Bringing together a number of genes or sequences from different sources may result in a nucleic acid sequence that is not functional in an organism. On the other hand, a single nucleic acid change which could be done by recombinant or synthetic means could lead to a significant enhancement in virulence. The focus of a biosafety analysis should be on the product with consideration of the source of the sequences. Synthetic techniques may result in a greater range of products than recombinant methods but the underlying challenge is the same: trying to understand how those disparate parts will act together. Ultimately a biological analysis of the end results will be required.

Under the current risk assessment framework of the *NIH Guidelines,* the starting point for any risk assessment begins with an assessment of the parent organism from which the sequence is derived. As discussed under Section II, Safety Considerations, synthetic techniques may enable the synthesis of more complex chimeras containing sequences from a number of different sources. This increasing complexity may make the task of determining the parent organism more challenging. This is addressed in proposed language that will be added to the risk assessment section of the *NIH Guidelines* (see proposed changes to Section II–A).

Therefore, the changes proposed below treat the biosafety risks of experiments that use recombinant and synthetic techniques as equivalent. Also, although it was recognized that synthetic genetic manipulation techniques are not necessarily a very recent development, the integration of other fields (for example, chemistry and engineering) may lead to rapid development of yet unknown products that may raise new biosafety risks not anticipated. The risk management framework being presented herein is based on the current science and that which appears to be feasible in the foreseeable future.

The amendments will broaden the scope of the *NIH Guidelines,* which currently cover research involving DNA molecules created via recombinant techniques (*i.e.*, joining of DNA molecules), to encompass nucleic acids that are synthesized chemically or by other means without the use of recombinant technology. As amended, the *NIH Guidelines* will apply to all nucleic acids. This is accomplished through changes in Section I–A, Purpose and Section I–B, Definition of Recombinant DNA Molecules. The required level of review will be based on the risk of the experiment, i.e. the risk to the laboratory worker, the public and the environment. Low risk basic research involving non-replicating synthetic nucleic acids will be exempt from the *NIH Guidelines* and from review at the local level. High risk basic and clinical studies may be subject to review by the RAC and the NIH. To effect these changes, four sections of the *NIH Guidelines* will be revised. The title of the document will be changed to *NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules* and throughout the *NIH Guidelines* the term recombinant DNA will be changed to recombinant and synthetic nucleic acids.

In addition to broadening the scope of the *NIH Guidelines* to encompass synthetic nucleic acids, included are proposed amendments to two other sections of the *NIH Guidelines,* Section III–A–1 and Section III–E–1, in order to (1) clarify the oversight of recombinant experiments involving the introduction of drug resistance traits and (2) to change the level of review for recombinant or synthetic experiments involving more than half but less than two-thirds of the genome of certain viruses in tissue culture. These proposed amendments were recommended by the RAC.

Section III–A–1 requires certain experiments involving the transfer of drug resistance traits to microorganisms to be reviewed by the RAC and approved by the NIH Director. The current language has raised concerns from IBCs and investigators seeking to identify those experiments that require this heightened review. The revisions to Section III–A–1 will clarify that all experiments involving the transfer of a drug resistance trait to a microorganism will be subject to RAC review and NIH Director approval if the microorganism's acquisition of the trait could compromise public health. The changes will clarify that the microorganism's ability to acquire the trait naturally is not relevant to the safety of the experiment, that the provisions apply even if the drug at issue is not considered the ''drug of choice,'' and that adverse effects on population subgroups need to be considered.

Under the *NIH Guidelines,* approval for an experiment under Section III–A is specific to the investigator submitting the proposal. Recognizing that this may not be an efficient use of resources and may slow important research, a new provision will authorize OBA to make a determination that a proposed experiment that would fall under Section III–A is equivalent to an experiment that has been reviewed previously as a Major Action and approved by NIH Director. In such cases, OBA will have the authority to permit this research to proceed without going through RAC review and NIH Director approval if OBA determines that there are no substantive differences in experimental design and pertinent information has not emerged since submission of the initial experiment that would impact on the biosafety or public health risks for the proposed experiments.

Section III–E–1 of the *NIH Guidelines* currently states that tissue culture experiments involving viral constructs that contain less than two-thirds of the genome of any one of the high risk viruses may be performed at the lowest containment level (Biosafety Level 1) and initiated upon registration with the local institutional biosafety committee. The change proposed to this section will increase the threshold to less than one-half of the viral genome and require evidence that the resulting nucleic acid molecules are not capable of producing a replication competent virus. These changes are prompted by an increased understanding of the biology of certain viruses for which there may be biosafety

risks for research involving less than two-thirds of the viral genome.

These recommendations were adopted unanimously by the RAC at its March 2008 meeting. Included in these proposed changes are targeted questions that were considered in developing the proposed revisions to the *NIH Guidelines.* NIH requests not only comments on the proposed changes but also comment on the specific issues raised by these questions.

It should be noted that the *NIH Guidelines* currently apply to research that is conducted at or sponsored by institutions that receive NIH funding for any research involving recombinant DNA. Due to these proposed changes, the *NIH Guidelines* will apply to research that is conducted at or sponsored by institutions that receive NIH funding for any research involving recombinant DNA and synthetic acid molecules. In addition, other, non-NIH, U.S. Government agencies, including the Department of Defense, the Department of Veterans Affairs and Department of Agriculture, currently have policies in place stating that all recombinant DNA research conducted by or funded by these agencies must comply with the *NIH Guidelines.* While the *NIH Guidelines* may not govern all Government funded research, it may be used as a tool for the entire research community to understand the potential biosafety implications of their research.

In reviewing the proposed changes it is important to understand that *NIH Guidelines* outline appropriate biosafety practices and containment measures for laboratory recombinant DNA (rDNA) research and govern the conduct of clinical trials that involve the deliberate transfer of rDNA, or DNA or RNA derived from rDNA, into human research participants. The focus of the *NIH Guidelines* is on the risks to laboratory workers, the public and the environment associated with rDNA research and if implemented, synthetic nucleic acid research. The *NIH Guidelines* do promote the use of biological containment through the application of highly specific biological barriers that may limit the infectivity, dissemination, or survival of recombinant agents outside the laboratory. Biological containment may, therefore, mitigate the consequences of intentional misuse of such agents but does not directly address biosecurity issues raised by deliberate exposure outside of a research setting. As revised, the *NIH Guidelines* will continue to focus on the biosafety aspects of research with recombinant and synthetic nucleic acid molecules.

There may also be biosecurity or dual use research concerns with some research involving recombinant or synthetic nucleic acid molecules, but that is beyond the scope of the *NIH Guidelines.* Biosecurity aspects of research involving infectious agents are addressed in other venues, including for example, in the CDC–NIH *Biosafety in Microbiological and Biomedical Laboratories,* 5th Edition (Section VI, Principles of Laboratory Biosecurity) and the Select Agent Rules (42 CFR 73, 9 CFR part 121 and 7 CFR part 131). In addition, the U.S.G. continues to address these issues. For example, the NSABB is developing recommendations for the oversight of dual use research and is also addressing the issue of personnel reliability among individuals working with select agents.

Proposed Amendments to the NIH Guidelines

In order to ensure that biosafety considerations of synthetic biology research are addressed appropriately, the NIH is proposing the following changes to the *NIH Guidelines:*

Title of the NIH Guidelines

The title of the document is proposed to be changed from the *NIH Guidelines for Research Involving Recombinant DNA Molecules to the NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules.*

Section I. Scope of the NIH Guidelines

In order to clarify the applicability of the *NIH Guidelines* to research involving synthetic nucleic acids (NA), the following modifications are proposed to Section I, Scope of the *NIH Guidelines.*

Section 1–A. Purpose

Section I-A (Purpose) of the *NIH Guidelines* currently states that: ''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.'' Section I–A is proposed to be amended to read: ''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 wholly or partially containing functional equivalents of nucleotides, or (iii) organisms and viruses containing such molecules.''

As a result of these modifications, the *NIH Guidelines* will clearly apply to both recombinant and synthetically derived nucleic acids, including those that contain functional analogs of nucleotides (*e.g.* , those used in artificially engineered genetic systems).

In accordance with this change in the scope of the *NIH Guidelines* the term ''recombinant DNA molecules'' will be replaced with ''recombinant and synthetic nucleic acid molecules.''

Section I–B. Definition of Recombinant and Synthetic Nucleic Acids

The current definition of recombinant DNA molecule in the *NIH Guidelines* (Section I–B) is limited because it only explicitly refers to DNA and requires that segments be joined, which may not need to occur in research with synthetic NAs. The proposed revisions to the definition would retain a definition of recombinant NA similar to the current one for recombinant DNA but also add synthetic NA created without joining of segments. The current definition of recombinant DNA in Section I–B of the *NIH Guidelines* is articulated in three paragraphs labeled as A, B, and C in this notice only. Paragraph A states: ''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.'' Paragraph B states: ''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.*'' Paragraph C states: ''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.''

The following modifications are proposed to Section I–B. Definition of Recombinant DNA Molecules: Paragraph A is proposed to be revised to read: ''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 nucleic acid molecules 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.''

Paragraph B will no longer be included in the definition. It was added to the *NIH Guidelines* in 1982 to clarify that then novel synthetic DNA segments would be considered as equivalent to their natural DNA counterparts with regards to containment conditions; however, it only covered synthetic DNA if it produced a toxin or a pharmacologically active agent. The language presented difficulty in interpretation because of the lack of definition of ''toxin or a pharmacologically active agent.'' Paragraph B is proposed to be deleted due to the fact that the concepts are sufficiently covered in the following portions: The new (ii) in paragraph A which explicitly extends the scope of the *NIH Guidelines* to cover recombinant and synthetic constructs, and Section III–F (Exempt Experiments) of the *NIH Guidelines,* which as discussed later, exempts those synthetic nucleic acid constructs that do not pose a significant biosafety risk.

Paragraph C will be deleted from this portion and will be moved to Section III–F of the *NIH Guidelines.* This is a proposed reorganization of the *NIH Guidelines* so that exempt molecules will be described in one place. A new Section IIIF–7 is proposed to read: ''Genomic DNA molecules of plants and bacteria that have acquired a transposable element provided the transposable element does not contain any recombinant or synthetic DNA'' are not subject to the *NIH Guidelines.*

In accordance with these changes in the scope and definition of the *NIH Guidelines,* the term ''recombinant DNA molecules'' will be replaced with ''recombinant and synthetic nucleic molecules'' throughout the *NIH Guidelines*.

Section III–C–1. Experiments Involving the Transfer of Recombinant DNA, or DNA or RNA Derived From Recombinant DNA, Into One or More Human Research Participants

In accordance with the change to the scope and definition of recombinant DNA, the definition of human gene transfer experiments will be amended. The first paragraph of Section III–C–1 currently states: ''For an experiment involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I–E–7) until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements).'' As amended the first paragraph will state: ''For an experiment involving the deliberate transfer of recombinant or synthetic nucleic acids into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I–E–7) until the RAC review process has been completed (see Appendix M–I–B, RAC Review Requirements).''

Section III–F. Exempt Experiments

Additional modifications are proposed to augment or clarify experiments that are exempt from the *NIH Guidelines*, those listed in Section III–F. The exemptions under Section III–F are designed to strike a balance between safety and overregulation. They exempt certain nucleic acid molecules from oversight by the *NIH Guidelines* because their introduction into a biological system is not expected to have a biosafety risk that requires review by an IBC or the introduction of these nucleic molecules into biological systems would be akin to processes that already occur in nature and hence determining proper biosafety practices would be evident by the characteristics of naturally occurring sequence and/or would be covered by other guidances. Is there a risk that these exemptions could inadvertently exempt an experiment that is deserving of IBC review? First, it is important to recognize that with the exception of the new proposed III–F–1 discussed below, the exemptions from the original *NIH Guidelines* have been preserved with minor modifications. While synthetic synthesis of nucleic acids will potentially raise new biosafety concerns the exemptions focus narrowly on a small set of products that should not raise biosafety concerns that warrant IBC review whether created by recombinant or synthetic means.

To emphasize that research exempt from the *NIH Guidelines* will still have biosafety considerations and that other standards of biosafety may apply, a modification is proposed to the introductory language. Section III–F currently states: ''The following recombinant DNA molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee is not required.'' This portion is proposed to read: ''The following recombinant and/or synthetic nucleic acids molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee is not required. However, other Federal and state standards of biosafety may still apply to such research (for example, the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories Manual).''

Section III–F–1

A new exemption under Section III–F–1 will exempt synthetic nucleic acids that cannot replicate from the *NIH Guidelines* unless they are used in human gene transfer (see Section III–C–1). This exemption is proposed so that the *NIH Guidelines* apply to synthetic NA research in a manner consistent with the current oversight of basic and preclinical recombinant DNA research. Currently oversight is limited to recombinant molecules that replicate or are derived from such molecules. The added section exempts basic, non-clinical research with synthetic NA that can not replicate or were derived from molecules that can replicate. The biosafety risks of using such constructs in basic and preclinical research are believed to be low. If a nucleic acid is incapable of replicating in a cell, any toxicity associated with that nucleic acid should be confined to that particular cell or organism and spread to neighboring cells or organisms should not occur to any appreciable degree. This type of risk is identical to that observed with chemical exposures, although nucleic acids are generally far less toxic than most chemicals.

Members of the RAC Biosafety Working Group noted that one of the original impetuses for creating a special biosafety oversight for recombinant DNA research was the novel biosafety risks to the individual laboratory worker, the public health, and the environment presented by the ability of novel replicating nucleic acids to disseminate and persist within and outside of the laboratory. This risk of transmissibility is distinct from chemicals or other toxins, because of the potential for long-term persistence.

Human gene transfer clinical trials should be differentiated from basic research. Current human gene transfer trials often involve non-replicating recombinant molecules. These are captured by the *NIH Guidelines* (see Section III–C–1 and Appendix M), because they are derived through recombinant technology that has steps involving replication (*e.g.*, replication incompetent vectors, RNAi or antisense RNA expressed from vectors are all derived from replicating systems). The biosafety and health risks for human gene transfer for synthetic non-replicating nucleic acids are not fundamentally different from non-replicating recombinant vectors.

The safety distinction between laboratory research and human gene

transfer is based on the difference in the potential health risk due to inadvertent lab exposure during basic or preclinical work and deliberate clinical gene transfer. The doses and routes of administration used in human gene transfer generally increase the risks. The risks to be considered for human gene transfer are not limited to the replicative nature of the vector but include transgene effects, risks of insertional mutagenesis, and immunological responses. For example, in the context of human gene transfer, the deliberate transfer of large numbers of replication incompetent retroviral vectors to hematopoietic stem cells in human clinical trials for X-Linked severe combined immunodeficiency disease contributed to the development of leukemia in some subjects starting several years after dosing. This is a unique situation in human trials that would not be replicated in a preclinical lab setting. Human gene transfer also raises scientific, medical, social and ethical considerations that warrant special attention and public discussion.

The following new exemption is proposed to be inserted as Section III–F–1; the current exemptions III–F–1 through III–F–5 are proposed to be re-numbered as III–F–2 through III–F–6. Section III–F–6 is proposed to become III–F–8, because a new section III–F–7 is proposed to be inserted. Section III–F–1 is proposed to read:

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).

In arriving at the conclusion that non-replicating synthetic nucleic acids pose limited risks to the public or environment, the RAC considered different types of potential experiments involving a range of possible exposures (*e.g.*, dose, route) and nucleic acids (*e.g.*, positive strand RNA viruses, replication incompetent integrating vectors). For most research, the risks were considered sufficiently low so that little benefit was considered to be gained by increased oversight, which may hinder research. However, some questions remained. The public is encouraged to submit written comments on the following questions raised by this proposed modification to distinguish between laboratory and clinical research with replicating and non-replicating NA molecules.

(1) Is there a sufficient distinction between the risks of basic and preclinical research with replicating vs. non-replicating synthetic molecules to warrant the exemption?

(a) What are the risks with the use of replication incompetent integrating vectors in the laboratory? For example, preclinical research with recombinant lentiviral vectors is covered by the current *NIH Guidelines* 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 as to warrant exemption from the *NIH Guidelines*?

(2) Since the increased risk associated with human gene transfer is in part related to the administration of higher doses, should the exemption be limited to experiments involving the handling of low quantities or doses of NAs? What quantity would not be expected to pose a biosafety risk?

(3) Are there examples of non-replicating, synthetic NA research that should not be exempt due to greater potential risks (*e.g.*, expression cassettes for oncogenes or toxins)?

(4) For human gene transfer research, are there classes of non-replicating molecules that should be exempt due to lower potential risks (*e.g.*, antisense RNA, RNAi, etc.)? If so, what criteria should be applied to determine such classes?

Section III–F–2

Section III–F–1 is proposed to be renumbered to III–F–2 and will be amended to clarify that replicating NAs that are not in cells (in addition to organisms and viruses) are exempt. Essentially, nucleic acids that are not in a biological system that will permit replication and that have not been modified to enable improved penetration of cell membranes are extremely unlikely to have biosafety risks.

The primary risks associated with all nucleic acids, whether synthetic or natural, are the effects these can engender when inside an organism or the cellular compartment. Nucleic acids can alter protein expression patterns in cells by binding to nucleic acids and blocking (1) replication of DNA, (2) transcription of DNA into RNA and (3) translation of RNA into protein. Furthermore, binding of synthetic or natural DNA to cellular nucleic acids may result in degradation of cellular DNA or RNA through the activity of natural cellular defense mechanisms. Natural or synthetic DNA may have catalytic activity (*e.g.*, ribozymes) that can cleave target sequences in nucleic acids. It is these effects that can potentially lead the cell or organism containing the nucleic acid to pose a risk to laboratory workers, the public or environment.

None of the effects described above will occur unless the nucleic acid is introduced into an organism, or a cell. Nucleic acids, by virtue of their physical and chemical properties do not readily penetrate cell membranes. The negative charge of a nucleic acid molecule effectively prevents transfer across the plasma membrane of a cell unless the negative charges of the molecule are either masked or neutralized by addition of chemical compounds (*e.g.,* cationic lipids, calcium phosphate) or the cell membrane is physically perforated (*e.g.,* electroporation) to enable penetration and uptake by the cell.

In practice, the current *NIH Guidelines* cover the introduction or modification of recombinant DNA in tissue culture, organisms and viruses. Therefore, for clarity and in recognition that techniques have developed to more readily permit introduction of nucleic acids into cells, the amended F–1 speaks to cells, organisms and viruses. In addition, as stated above, natural barriers exist for entry of unmodified nucleic acids into cells. However, manipulation of molecules modified for improved penetration of cell membranes in the laboratory may have increased risk due to the enhanced ability to penetrate cell membranes and thus be able to replicate. Therefore, section III-F–1 is being modified to address such modified nucleic acids as well.

Specifically, Section III–F–1 is proposed to be renumbered as III–F–2 and amended as follows:

The current Section III–F–1 states: ''Those that are not in organisms or viruses.''

Section III–F–1 will be re-numbered to III–F–2 and is proposed to be amended to: ''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.''

The proposed Sections III–F–3 through III–F–7 retain exemptions that were in the original *NIH Guidelines* with minor revisions. In reviewing these exemptions it is important to understand that it is not the goal of the *NIH Guidelines* to regulate all nucleic acid research but rather that subset of research that through recombinant or now synthetic means results in unique organisms or cells that potentially possess characteristics not yet seen in nature and hence pose potential safety risks both to the individual as well as

the community should there be an inadvertent release. Specifically, the molecules that fall under the new Section III–F–3 (formerly Section III–F–2) are those that consist solely of the exact nucleic acid sequence from a single source that exists contemporaneously in nature. Those described in the new Sections F–4 and F–5 (formerly Sections F–3 and F–4) are nucleic acids that are being propagated in a host that is either the natural host for such nucleic acids or is a closely related prokaryotic or eukaryotic host. Again such constructs may already exist outside of a laboratory. Research that falls under F–6 (formerly Section F–5) is exempt because the manipulation of these nucleic acids in a laboratory setting would be equivalent to that which occurs in nature when certain organisms exchange genetic material via physiological processes (*e.g.*, bacterial mating) outside of a laboratory setting. It is limited to those organisms that are already known to exchange DNA in nature. Finally, research that falls under the proposed Section F–7 also involves a natural physiological process, i.e., transposition. Transposons are nucleic acid molecules that exist in a wide variety of organisms from bacteria to humans. These molecules have the ability to move from one portion of an organism's genome to another. This new Section of III–F captures what was previously an exemption to the definition in the *NIH Guidelines* of a recombinant DNA molecule. Unless a transposon has been modified to be a recombinant molecule, genomic DNA of either plants or bacteria that has acquired a transposon is not subject to the *NIH Guidelines.* This is because if these transposons have not been modified by the insertion of recombinant or synthetic DNA, they are equivalent to what is already in nature and the process occurs naturally outside of lab.

The following changes are proposed for the Section III–F exemptions.

Section III–F–3

Section III–F–2 is proposed to be re-numbered to III–F–3 and amended. In the current *NIH Guidelines,* research with molecules from a single DNA source is exempt. This would include molecules containing duplications or deletions; however, such molecules may present different risks than those of the wild type parent agents. The revised language is intended to clarify that exempt molecules must have the exact nucleic acid sequence from an organism that currently exists in nature in order to be exempt (*e.g.*, because the 1918 influenza no longer exists in nature, research involving the reconstructed virus would not qualify for this exemption). The exemption does not imply that there are no biosafety risks associated with such research but rather recognizes that the *NIH Guidelines* do not apply to wild-type strains currently found in nature because a risk assessment for such work can be made with reference to the biological characteristics of the wild-type organism and are covered by other NIH biosafety standards (for example CDC/NIH Biosafety in Microbiological and Biomedical Laboratories Manual).

The following modifications are proposed for Section III–F–2. Section III–F–2 is proposed to be re-numbered to III–F–3 and amended as follows:

The current III–F–2 states: ''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.'' III–F–2 is proposed to be renumbered to III–F–3 and is proposed to be amended to state: ''Recombinant or synthetic nucleic acids that consist solely of the exact nucleic acid sequence from a single source that exists contemporaneously in nature.''

This proposed modification would change ''single nonchromosomal or viral source'' to simply ''single source.'' Specific comment is requested as to whether it is sufficiently clear that single source refers to ''single chromosomal, non-chromosomal, or viral NA source'' or should the language be specifically spelled out?

Section III–F–4

The current Section III–F–3 is proposed to be renumbered to Section III–F–4 and amended. Section III–F–3 states: ''Those that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means.'' It is proposed to be amended as follows: ''Section III–F–4. Those that consist entirely of nucleic acids from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means.''

Section III–F–5

The current Section III–F–4 is proposed to be renumbered to Section III–F–5. Section III–F–4 currently states: ''Those that consist entirely of DNA from a eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).'' It is proposed to state the following: ''Section III–F–5: Those that consist entirely of nucleic acids from a eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).''

Section III–F–6

The current Section III–F–5 is proposed to be renumbered to Section III–F–6. The current Section III–F–5 states: ''Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the NIH Director with advice of the RAC after appropriate notice and opportunity for public comment (*see* Section IV–C–1–b–(1)–(c), Major Actions). See Appendices A–I through A–VI, Exemptions Under Section III–F–5—Sublists of Natural Exchangers, for a list of natural exchangers that are exempt from the *NIH Guidelines*.'' It is proposed to be amended to state: ''Section III–F–6. Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the NIH Director with advice of the RAC after appropriate notice and opportunity for public comment (*see* Section IV–C–1–b–(1)–(c), Major Actions). See Appendices A–I through A–VI, Exemptions Under Section III–F–6–Sublists of Natural Exchangers, for a list of natural exchangers that are exempt from the *NIH Guidelines.*'' Additionally, Appendix A1–through A–VI will be amended to reference Section III–F–6 rather than III–F–5.

Section III–F–7

A new Section III–F–7 is proposed to be added. This proposed new Section takes an exemption that was previously included in the original definition (Section I–B) and moves it to this Section so that the definition of recombinant and nucleic acids found in the proposed Section I–B is solely a definition and does not include exemptions. The proposed exemption language has been simplified to make it clear that unmodified transposons used in research are not subject to the *NIH*

Guidelines even if derived from a recombinant or synthetic system. Section I–B: Genomic DNA molecules 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. New Section III–F–7 is proposed to state:

Section III–F–7. Genomic DNA molecules of plants and bacteria that have acquired a transposable element provided the transposable element does not contain any recombinant or synthetic DNA.

Section III–F–8

The current Section III–F–6 is proposed to be renumbered to Section III–F–8 and amended. This section provides a mechanism for the NIH Director to expand the exemptions to molecules not covered elsewhere in Section III–F. Research that falls under Section III–F–8 would need to have been reviewed and approved by the NIH Director following advice from the RAC and notice in the **Federal Register** to provide an opportunity for public comment. Only research that has been deemed to not present, following this extensive review process, a significant risk to health or the environment would fall under this section.

Current Section III–F–6 states: ''Those that do not present a significant risk to health or the environment (see Section IV–C–1–b–(1)–(c), Major Actions), as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment. See Appendix C, Exemptions under Section III–F–6 for other classes of experiments which are exempt from the *NIH Guidelines.*'' Section III–F–6 is proposed to be amended to state: ''Section III–F–8. Those that do not present a significant risk to health or the environment (*see* Section IV–C–1–b–(1)–(c), Major Actions), as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment. See Appendix C, Exemptions under Section III–F–8 for other classes of experiments which are exempt from the *NIH Guidelines.*'' Additionally Appendix A1– through A–VI will be amended to reference Section III–F–8 rather than III–F–6.

Section III–E–1. Experiments Involving the Formation of Recombinant DNA Molecules Containing No More Than Two-Thirds of the Genome of Any Eukaryotic Virus

Experiments covered by Section III–E–1 can be initiated using Biosafety Level (BL) 1 containment simultaneously with Institutional Biosafety Committee notice. Section III–E–1 currently states: ''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, *Experiments Involving the Use of Infectious Animal or Plant DNA or RNA viruses or Defective Animal or Plant DNA or RNA viruses in the Presence of Helper Virus in Tissue Culture Systems,* 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.''

This section applies to viral constructs containing less than ⅔ of the genome of any virus (with all viruses from a single Family being considered as identical). However, concerns were raised that this level of oversight may not be adequate for research with potential synthetic biology agents derived from multiple segments of NA from a Family of viruses. In addition, some wild type viruses (*e.g.*, herpes viruses) may be functional with less than ⅔ of the genome present. Therefore, the decision was made to propose to change ⅔ to one-half of the genome to reflect the current understanding of the biology of certain viruses. While the use of a quantitative measure to define properties of biological organisms is imperfect, the more conservative standard is consistent with Appendix C–1 *Recombinant DNA in Tissue Culture* which exempts from the *NIH Guidelines* recombinant DNA molecules from Risk Groups 1 and 2 that contain less than one-half of any eukaryotic viral genome. With this revision, experiments involving risk Group 3 and 4 viruses with less than one-half of any eukaryotic viral genome can be initiated at BL1 containment simultaneously with IBC registration provided evidence is also submitted attesting that the preparation(s) are free of replication competent virus, which may be generated through homologous recombination with endogenous proviruses or the use of a helper virus. If revised as proposed, an investigator will be permitted to initiate an experiment simultaneously with registration, since the retention of a quantitative standard provides such clear guidance.

Section III–E–1 is proposed to be amended to state: ''Recombinant and synthetic nucleic acid 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 BL1 containment (as defined in Appendix G) provided there is evidence that the resulting nucleic acid in these cells are not capable of producing a replication competent nucleic acid. 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, *Experiments Involving the Use of Infectious Animal or Plant DNA or RNA viruses or Defective Animal or Plant DNA or RNA viruses in the Presence of Helper Virus in Tissue Culture Systems* should be used. The nucleic acids may contain fragments of the genome of viruses from more than one Family but each fragment shall be less than one-half of a genome.''

Section IV–A Policy

Section IV–A concerns the roles and responsibilities of the local institutions and investigators in implementing the *NIH Guidelines.* It contains a general policy statement that is often evoked as the ''spirit'' of the *NIH Guidelines* because it acknowledges the inability of the document to describe specifically all conceivable research or emerging techniques; however, it remains the responsibility of researchers and institutions to adhere to ''the intent of the *NIH Guidelines* as well as to their specifics.'' In order to emphasize that the *NIH Guidelines* are an evolving document which are expected to be modified to address new developments in research or scientific techniques, the following modifications are proposed to Section IV–A (Policy).

Section IV–A currently states: ''The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. The *NIH Guidelines* cannot anticipate every possible situation. Motivation and good judgment are the key essentials to protection of health and the environment. The *NIH Guidelines* are intended to assist the institution, Institutional Biosafety Committee, Biological Safety Officer, and the Principal Investigator in determining

safeguards that should be implemented. 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. Each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in compliance with the *NIH Guidelines*. General recognition of institutional authority and responsibility properly establishes accountability for safe conduct of the research at the local level. The following roles and responsibilities constitute an administrative framework in which safety is an essential and integral part of research involving recombinant DNA molecules. Further clarifications and interpretations of roles and responsibilities will be issued by NIH as necessary.''

Section IV–A is proposed to be amended to read: ''The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. The *NIH Guidelines* cannot anticipate every possible situation. Motivation and good judgment are the key essentials to protection of health and the environment. The *NIH Guidelines* are intended to assist the institution, Institutional Biosafety Committee, Biological Safety Officer, and the Principal Investigator in determining safeguards that should be implemented. 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 yet yielded organisms that present safety concerns that fall outside the current risk assessment framework used for recombinant DNA 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 determine whether revisions to the *NIH Guidelines* are needed. As new techniques develop, the *NIH Guidelines* should be periodically reviewed to determine whether and how such research should be explicitly addressed. 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. Therefore, each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant and/or synthetic nucleic acids research conducted at or sponsored by that institution is conducted in compliance with the *NIH Guidelines*. General recognition of institutional authority and responsibility properly establishes accountability for safe conduct of the research at the local level. The following roles and responsibilities constitute an administrative framework in which safety is an essential and integral part of research involving recombinant and/or synthetic nucleic acid molecules. Further clarifications and interpretations of roles and responsibilities will be issued by NIH as necessary.''

Section II. Safety Considerations

Currently, the risk assessment framework of the *NIH Guidelines* uses the risk group of the parent organism as a starting point for determining the necessary containment level. For example, genetic modifications using a Risk Group 3 organism (defined as agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available) would generally be carried out at BL3 but the containment level might be raised or lowered depending on the specific construct and the experimental manipulations. The RAC concluded that the current risk assessment framework under the *NIH Guidelines* is applicable to experiments with synthetic nucleic acids. However, additional language is proposed to provide further guidance for evaluating research utilizing the capabilities of synthetic biology, as use of these techniques may lead to the creation of complex organisms for which identification of a parent organism, the starting point of the existing recombinant DNA risk assessment, is more difficult. Risk assessment may also be complicated by the limitations in predicting function from sequence(s) or the synergistic effects from combining sequences from different sources in a novel context.

Section II–A–3 (Comprehensive Risk Assessment) currently states:

''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. The Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments described in Sections III–A, *Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation;* III–B, *Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation;* III–C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/OBA Registration Before Initiation;* III–D, *Experiments that Require Institutional Biosafety Committee Approval Before Initiation.*

Careful consideration should be given to the types of manipulation planned for some higher Risk Group agents. For example, the RG2 dengue viruses may be cultured under the Biosafety Level 2 (BL2) containment (see Section II–B); however, when such agents are used for animal inoculation or transmission studies, a higher containment level is recommended. Similarly, RG3 agents such as Venezuelan equine encephalomyelitis and yellow fever viruses should be handled at a higher containment level for animal inoculation and transmission experiments.

Individuals working with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or other bloodborne pathogens should consult the applicable Occupational Safety and Health Administration regulation, 29 CFR 1910.1030, and OSHA publication 3127 (1996 revised). BL2 containment is recommended for activities involving all blood-contaminated clinical specimens, body fluids, and tissues from all humans, or from HIV- or HBV-infected or inoculated laboratory animals. Activities such as the production of research-laboratory scale quantities of HIV or other bloodborne pathogens, manipulating concentrated virus preparations, or conducting procedures that may produce droplets or aerosols, are performed in a BL2 facility using the additional practices and containment equipment recommended for BL3. Activities involving industrial scale volumes or preparations of concentrated HIV are conducted in a BL3 facility, or BL3 Large Scale if appropriate, using BL3 practices and containment equipment.

Exotic plant pathogens and animal pathogens of domestic livestock and poultry are restricted and may require special laboratory design, operation and containment features not addressed in *Biosafety in Microbiological and Biomedical Laboratories* (*see* Section V–C, *Footnotes and References of Sections I through IV*). For information regarding the importation, possession, or use of these agents see Section V–G and V–H, *Footnotes and References of Sections I through IV*.''

The first three paragraphs are proposed to be amended by inserting the following two new paragraphs between the current first and second paragraphs of Section II–A–3:

''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*).

While the initial risk assessment is based on the identification of the Risk Group 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 involves a consideration of the Risk Groups 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 risk group 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 all sequences will function as predicted in the original host context.

The IBC must also be cognizant that the combination of certain sequences may result in an 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 biosafety risk may occur with a chimera formed through combination of sequences from a number of organisms or due to the synergistic effect of combining transgenes that results in a new phenotype.

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. The Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments described in Sections III–A, *Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation;* III–B, *Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation;* III–C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/OBA Registration Before Initiation;* III–D, *Experiments that Require Institutional Biosafety Committee Approval Before Initiation*.''

Section III-A–1. Major Actions Under the NIH Guidelines

In reviewing the biosafety risks for synthetic genomics and biology and the different levels of review for each experiment, the RAC determined that it is important to also evaluate the class of experiments that require the highest level of review. In doing so, it was determined that the language for Section III–A–1 of the *NIH Guidelines* (research involving the introduction of drug resistance) does not clearly articulate the types of experiments that warrant this heightened review. Moreover, given the change in the use of antibiotics and the public health problems raised by the emergence of multi-drug resistant bacterial strains, clearly defining those experiments that require heightened review is a public health priority.

Section III–A–1-a currently states: ''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.''

Section III–A–1-a is proposed to be amended to: ''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). Even if an alternative drug or drugs exist for the control or management of disease, it is important to consider how the research might affect the ability to control infection in certain groups or subgroups by putting them at risk of developing an infection by such microorganism for which alternative treatments may not be available. Affected groups or subgroups may include, but are not limited to: children, pregnant women, and people who are allergic to effective alternative treatments, immunocompromised or living in countries where the alternative effective treatment is not readily available.''

The deletion of the phrase ''that are not known to acquire the trait naturally'' is proposed because the mechanism of acquisition should not be relevant as to whether these experiments pose potential public health risk and as such

should receive a higher level of review. Moreover, all forms of antibiotic resistance occur naturally and the use of antibiotics creates selective pressure for resistant strains. The additional text recognizes that a drug may remain useful for control of a disease despite some percentage of the population of microorganisms having developed resistance. It is also intended to clarify that even if a particular drug is not considered the ''drug of choice'' to treat a disease, elimination of such a drug as a treatment option may still raise important clinical and public health considerations for certain subpopulations.

Once a Section III–A–I–a experiment is reviewed by the RAC and approved by the NIH Director, equivalent experiments may not need to follow the same approval process to determine the appropriate biosafety containment level for the work. A new section under III–B (Experiments that Require NIH/OBA and IBC Approval before Initiation) is proposed to be added to allow NIH/OBA the discretion to review and approve certain experiments if NIH/OBA determines that an equivalent experiment has already been approved by the NIH Director and there are no substantial changes to the proposed experiment or new information that would raise new biosafety or public health issues. Under this proposal, Investigators will be notified by NIH/OBA if such a determination has been made.

The following addition is proposed to be added to Section III–B of the *NIH Guidelines* to allow NIH/OBA 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–2, *Experiments that have been approved (under Section III–A–1–a) as Major Actions under the NIH Guidelines*

Upon receipt and review of an application from the investigator, 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. An experiment will only be considered equivalent if, as determined by NIH/OBA, there are no substantive differences in experimental design or pertinent information has not emerged since submission of the initial III–A–1 experiment that would impact on the biosafety or public health risks for the proposed experiments. If such a determination is made by NIH/OBA, these experiments will not require review and approval under Section III–A.''

Dated: February 26, 2009.

Amy P. Patterson,

Acting Director, Office of Science Policy, National Institutes of Health.

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DEPARTMENT OF HOMELAND SECURITY

Coast Guard

[USCG–2008–0929]

Collection of Information Under Review by Office of Management and Budget: OMB Control Numbers: 1625–0040

AGENCY: Coast Guard, DHS.

ACTION: Thirty-day notice requesting comments.

SUMMARY: In compliance with the Paperwork Reduction Act of 1995, this request for comments announces that the U.S. Coast Guard is forwarding an Information Collection Request (ICR), abstracted below, to the Office of Information and Regulatory Affairs (OIRA), Office of Management and Budget (OMB) requesting a revision of their approval for the following collection of information: 1625–0040, Continuous Discharge Book, Application, Physical Exam Report, Sea Service Report, Chemical Testing, Entry Level Physical. Our ICR describes the information we seek to collect from the public. Review and comments by OIRA ensure we only impose paperwork burdens commensurate with our performance of duties.

DATES: Please submit comments on or before April 3, 2009.

ADDRESSES: You may submit comments identified by Coast Guard docket number [USCG–2008–0929] to the Docket Management Facility (DMF) at the U.S. Department of Transportation (DOT) or to OIRA. To avoid duplication, please submit your comments by only one of the following means:

(1) *Electronic submission.* (a) To Coast Guard docket at *http://www.regulation.gov.* (b) To OIRA by e-mail via: *oira_submission@omb.eop.gov*.

(2) *Mail or Hand delivery.* (a) DMF (M–30), DOT, West Building Ground Floor, Room W12–140, 1200 New Jersey Avenue, SE., Washington, DC 20590–0001. Hand deliver between the hours of 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. The telephone number is 202–366–9329. (b) To OIRA, 725 17th Street, NW., Washington, DC 20503, to the attention of the Desk Officer for the Coast Guard.

(3) *Fax.* (a) To DMF, 202–493–2251. (b) To OIRA at 202–395–6566. To ensure your comments are received in time, mark the fax to the attention of the Desk Officer for the Coast Guard.

The DMF maintains the public docket for this Notice. Comments and material received from the public, as well as documents mentioned in this Notice as being available in the docket, will become part of the docket and will be available for inspection or copying at room W12–140 on the West Building Ground Floor, 1200 New Jersey Avenue, SE., Washington, DC, between 9 a.m. and 5 p.m., Monday through Friday, except Federal holidays. You may also find the docket on the Internet at *http://www.regulations.gov.*

A copy of the complete ICR is available through the docket on the Internet at *http://www.regulations.gov.* Additionally, copies are available from Commandant (CG–611), U.S. Coast Guard Headquarters (Attn: Mr. Arthur Requina), 2100 2nd Street, SW., Washington, DC 20593–0001. The telephone number is 202–475–3523.

FOR FURTHER INFORMATION CONTACT: Mr. Arthur Requina, Office of Information Management, telephone 202–475–3523 or fax 202–475–3929, for questions on these documents. Contact Ms. Renee V. Wright, Program Manager, Docket Operations, 202–366–9826, for questions on the docket.

SUPPLEMENTARY INFORMATION: The Coast Guard invites comments on whether this ICR should be granted based on it being necessary for the proper performance of Departmental functions. In particular, the Coast Guard would appreciate comments addressing: (1) The practical utility of the collections; (2) the accuracy of the estimated burden of the collections; (3) ways to enhance the quality, utility, and clarity of information subject to the collections; and (4) ways to minimize the burden of collections on respondents, including the use of automated collection techniques or other forms of information technology.

Comments to Coast Guard or OIRA must contain the OMB Control Number of the ICR. Comments to Coast Guard must contain the docket number of this request, [USCG 2008–0929]. For your comments to OIRA to be considered, it is best if they are received on or before April 3, 2009.

Public participation and request for comments: We encourage you to respond to this request by submitting comments and related materials. We will post all comments received,