Applicability of the Select Agent Regulations to Issues of Synthetic Genomics

In a December 2006 report entitled "Addressing Biosecurity Concerns Related to the Synthesis of Select Agents" (www.biosecurityboard.gov/links.asp), the National Science Advisory Board on Biosecurity recommended that the Federal government take steps to "Increase awareness among providers and users of synthetic genomic materials regarding compliance with the select regulations; and provide a list of genomic materials explicitly covered by the regulations."

The purpose of this document is to provide guidance regarding the application of the current select agent regulations to those who create and use synthetic genomic products. The current select agent regulations implement the provisions of the Agricultural Bioterrorism Act of 2002 and the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. Select agents are bacteria, viruses, fungi, other microorganisms and toxins that have been deemed to have the potential to pose a significant risk to public health, plant or animal health, or plant or animal production. Regulation of the possession, use, and transfer of select agents is implemented by the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA/APHIS) and the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (HHS/CDC). Individuals applying for access to select agents must undergo a security risk assessment by the Federal Bureau of Investigation, Criminal Justice Information Service (FBI/CJIS). Information on the select agent regulations (42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331) can be found at the national select agent website (www.selectagents.gov).

The select agent regulations provide that the following genetic elements, recombinant nucleic acids, and recombinant organisms are select agents (See section 3(c) of 42 CFR Part 73, 9 CFR Part 121, and 7 CFR Part 331):

- Nucleic acids that can produce infectious forms of any of the select agent viruses.
- Recombinant nucleic acids that encode for the functional form(s) of select agent toxins if the nucleic acids:
    - Can be expressed *in vivo* or *in vitro* or,
    - Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.
- Select agents and toxins that have been genetically modified.

The purpose of this regulatory language is to address advancements in molecular biology that may influence the production of infectious forms of select agent viruses, or the active forms of select agent toxins. It has been demonstrated, for example, that the single stranded (positive strand) RNA viruses and certain double stranded DNA viruses that utilize host polymerases contain nucleic acids that can produce infectious forms. Examples of select agent viruses that meet this criterion, and would therefore be regulated, include:

- Tickborne encephalitis complex (flavi) viruses:
    - Central European Tick-borne encephalitis
    - Far Eastern Tickborne encephalitis

        - Russian Spring and Summer encephalitis
        - Kyasanur Forest Disease
        - Omsk Hemorrhagic Fever
    - Eastern Equine Encephalitis virus
    - Venezuelan Equine Encephalitis virus
    - Classical Swine Fever Virus
    - Foot-And-Mouth Disease Virus
    - Japanese Encephalitis Virus
    - Swine Vesicular Disease Virus
    - Cercopithecine Herpesvirus 1 (Herpes B virus)
    - Malignant Catarrhal fever Virus (Alcelaphine Herpesviurs Type 1)

Under the current select agent regulations the following are examples of materials that would not be regulated as a select agent:

- Non-infectious components of select agent viruses including:
    - Material from regulated genomes that has been rendered non-infectious
    - cDNA made from regulated select agent genomes
    - Genomic fragments from select agents (unless they encode for a functional form of a select agent toxin)
    - Complete genomes of single-stranded negative strand RNA viruses, double stranded RNA viruses, and double-stranded DNA viruses that require a unique polymerase (Variola major virus*, Monkeypox virus, African swine fever virus, Camel pox virus, Goat pox virus, lumpy skin disease virus, and Sheep pox virus)
    - Genomic material from select agent bacteria or fungi

      (*It should be noted that, although the current select agent regulations to not apply to Variola major genetic elements, the World Health Organization places significant restrictions on the possession, use, and transfer of these materials. Institutions other than the two currently recognized WHO collaborating centers may not possess genetic fragments exceeding 20% of the Variola virus genome. For additional information on WHO Guidelines for Variola virus research, please see http://www.who.int/csr/disease/smallpox/research/en/index.html, and the report, also published in the Weekly Epidemiologic Record in 2008, on permissible use of variola genetic material http://www.who.int/csr/disease/smallpox/SummaryrecommendationsMay08.pdf)

- Genomic material from select agent strains that have been excluded from regulation under section 3(e) of the select agent regulations

Additionally, select agent nucleic acid sequence information is not regulated.

Individuals or entities that possess, use, or transfer select agents must meet all of the requirements of the select agent regulations (42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121) prior to possession, use, or transfer. These regulations, the associated enabling legislation,

related guidance documents, registration forms, and contact information for the Select Agent Programs can be found at the National Select Agent Registry website (www.selectagents.gov).

The following examples, while not inclusive of all potential scenarios, illustrate the application of the current select agent regulations to activities involving synthetic genomics or synthetic biology.

Example scenarios involving synthetic genomic select agent materials.

1. An individual submits to a producer (facility that manufactures the material) a full genome sequence of Foot-and-Mouth Disease Virus (FMDV) and requests that it be synthesized and shipped to the submitter (individual that requests the material).
   - Does the processing of this order fall under the current select agent regulations?

     Yes. An individual or entity in possession of the full FMDV genome, regardless of how the individual or entity came into possession of it, or for however brief a time period, would be required to be pre-registered under provisions of the select agent regulations, meeting all of the safety, security and personnel reliability requirements therein. Transfer of the full FMDV genome would require prior approval from the select agent program.

   - Does the sequence information that this individual submitted fall under the current select agent regulations?

     No. The current regulations do not cover sequence information.

   - The producer is registered with the Select Agent Program for possession of infectious FMDV genomic material. Once this material is produced, can the producer send it to the submitter?

     Yes, with stipulations. First, the submitter must also be registered with the Select Agent Program to possess select agents. Second, all domestic transfers of select agents must be preauthorized by either the CDC or APHIS Select Agent Program. All international exports must be preauthorized by the Department of Commerce. Since the producer is registered with the Select Agent Program, the Program must first authorize the domestic transfer. Instructions and forms for use in obtaining this authorization are available on the National Select Agent Registry website (www.selectagents.gov).

2. An individual submits an unidentified sequence to a producer and asks for its synthesis. Screening of this sequence by the producer shows a high degree of homology with the pXO2 virulence-associated plasmid of *Bacillus anthracis*.

   - Does the processing of this order fall under the current select agent regulations?

     No. Although *B. anthracis* organisms are regulated, the current regulations do not cover individual *B. anthracis* genetic elements. Unless the functional form of a select agent toxin is included in the product, select agent bacterial genomic material is not covered by the current regulations. However, all international exports of *B. anthracis* genetic elements associated with pathogenicity must be preauthorized by the Department of Commerce. Instructions for obtaining an export license are

available on the Bureau of Industry and Security website, www.bis.doc.gov.

3. An individual submits a genomic sequence for *Y. pestis* and asks for its synthesis.

   - Does the processing of this order fall under the current select agent regulations?

     No. Unless the functional form of a select agent toxin is included in the product, select agent bacterial and fungal genomes are not covered under the regulations. However, all international exports of *Y. pestis* genetic elements associated with pathogenicity must be preauthorized by the Department of Commerce. Instructions for obtaining an export license are available on the Bureau of Industry and Security website, www.bis.doc.gov.

4. An investigator in Canada submits an order for the synthesis and delivery to Canada of the genome of the Omsk Hemorrhagic Fever virus from a producer located in the United States.

   - Does the processing of this order fall under the current select agent regulations?

     Yes. The possession of this material is regulated by the select agent regulations and the entity performing the synthesis would have to be registered with the Select Agent Program. However, because the material is to be exported, it will require an export license from the U.S. Department of Commerce, Bureau of Industry and Security instead of a Select Agent Program authorization. Instructions for obtaining this license are available on the Bureau of Industry and Security website, www.bis.doc.gov.

5. A foreign national works at a laboratory and is trained to grow Eastern Equine Encephalitis virus (EEE) in order to produce a vaccine.

   - Does this activity fall under the current select agent regulations?

     Yes. The facility housing this work would have to be registered with the Select Agent Program and the foreign national involved in this work would have to have a clear Select Agent Security Risk Assessment in order to access the virus. In addition, there are "deemed export" licensing requirements from the Department of Commerce for the transfer of production technology to the foreign national working in the United States. An export license is required to transfer the technology to produce the EEE (1E001). Even though the final end use is a vaccine which is controlled under 1C991, the technology involves the virus strain and thus controlled. Instructions for obtaining an export license are available on the Bureau of Industry and Security website, www.bis.doc.gov.

6. A synthetic genomics producer located outside the U.S. receives an order from a laboratory within the U.S. for the genome of the Russian Spring and Summer encephalitis

virus.

- Does this activity fall under the current select agent regulations?

  Yes, in part. Although the producer is not required to follow the select agent regulations, the receiving laboratory must be registered with the Select Agent Program. In addition, the receiving laboratory must obtain an import permit from the CDC's Etiologic Agent Import Permit Program prior to importing this material. Information on obtaining import permits can be obtained from the National Select Agent Registry website (www.selectagents.gov).