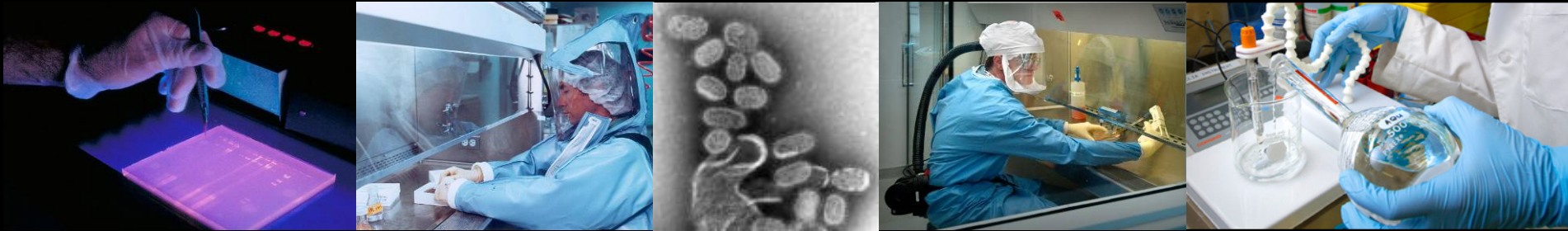


Select Agent Rules: *Intent and Interpretation of Controls for Select Agent Nucleotides*



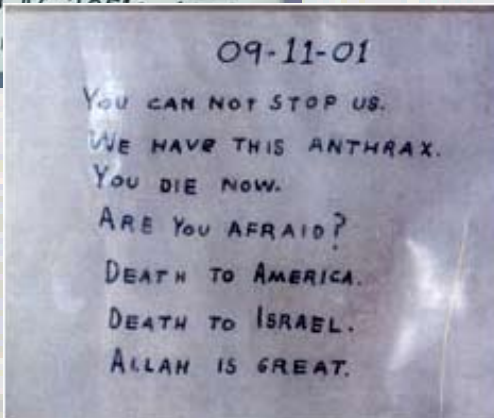
Mark Hemphill, M.S.
Chief of Policy

Division of Select Agents & Toxins

**Coordinating Office for Terrorism Preparedness and Emergency Response
Centers for Disease Control and Prevention**

July 13, 2006





Post - September 11, 2001

USA PATRIOT Act

(Uniting and Strengthening America by Providing Appropriate Tools
Required to Intercept and Obstruct Terrorism Act of 2001)

Public Law 107-56; Signed: 10/23/2001

Sec. 175b. Possession by Restricted Persons

- No restricted person shall ship, possess, or receive a Select Agent.
 - Under indictment or convicted of crime > 1 yr or is a fugitive from justice
 - Unlawful user of any controlled substance
 - Alien illegally or unlawfully in U.S.
 - Has been adjudicated as a mental defective or has been committed to any mental institution
 - Dishonorable discharge from Armed Services
 - Is an alien who is a national of a country that Sec. of State has made a determination has provided support for acts of international terrorism

Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and Agricultural Bioterrorism Protection Act of 2002

Public Law 107-188, Signed: June 12, 2002

- **Title II – Enhancing Controls on Dangerous Biological Agents and Toxins**
 - **Subtitle A – DHHS (Sec. 201-204)**
 - **Subtitle B – USDA (Sec. 211-123)**
 - **Subtitle C – Interagency Coordination Regarding Overlap Agents and Toxins (Sec. 221)**
 - **Subtitle D – Criminal Penalties (Sec. 231)**



Public Health Security and Bioterrorism Preparedness and Response Act of 2002

Public Law 107-188, Signed: June 12, 2002

- Significantly changed the regulatory authorities of HHS under Sec. 511 of the “Antiterrorism and Effective Death Penalty Act of 1996.”
- Granted comparable regulatory authorities to USDA for biological agents and toxins that present a severe threat to plant or animal health, or animal or plant products.
- Required coordination/concurrence between USDA and HHS on select agents and toxins regulated by both agencies
 - “Overlap” agents and toxins



Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and Agricultural Bioterrorism Protection Act of 2002

Public Law 107-188, Signed: June 12, 2002

Summary:

- Maintain a list of each biological agent and toxin (i.e., select agent and toxin) that has the potential to pose a severe threat to:
 - Public health and safety, or
 - Animal or plant health, or to animal or plant products
- Review select agents and toxins on the list every 2 years



Criteria to Consider



- The effect of exposure to the agent or toxin on:
 - Human health;
 - Animal or plant health, and on the production and marketability of animal or plant products
- The degree of contagiousness or pathogenicity of the agent or toxin and the methods by which the agent or toxin is transferred to:
 - Humans
 - Animals or plants
- The availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin

Public Health Security and Bioterrorism Preparedness and Response Act of 2002

Public Law 107-188, Signed: June 12, 2002

Requires:

- Registration for the possession, use, and transfer select agents and toxins
- Electronic database check by DOJ
 - Entity and individual
 - Restricted persons (USA PATRIOT Act)
- Establish requirements for safety
 - Proper training and laboratory facilities
- Establish requirements for security
 - To prevent access to such agents and toxins for use in terrorism
 - Or for any other criminal purpose

Public Health Security and Bioterrorism Preparedness and Response Act of 2002

Public Law 107-188, Signed: June 12, 2002

Summary:

- Specifies exemptions
- Additional criminal penalties
- Maintain availability of biological agents and toxins for research, education, and other legitimate purposes.

Federal Agencies Charged with Regulatory Oversight of Select Agents



Department of Health and Human Services

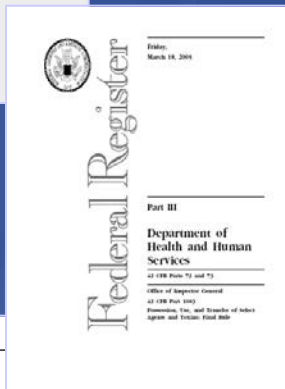
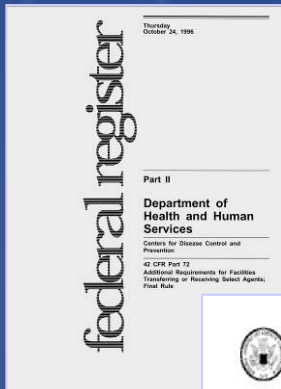
- Centers for Disease Control and Prevention
 - Coordinating Office for Terrorism Preparedness and Emergency Response
 - Division of Select Agents and Toxins

U.S. Department of Agriculture

- Animal and Plant Health Inspection Service
 - National Center for Import and Export
- Select Agent Program:
- Organisms and Vectors and Animals
 - Plant Protection and Quarantine (PPQ)



What are the Select Agent Regulations?



- Interim Final Rule: “Possession Use, and Transfer of Select Agents and Toxins” (42 C.F.R. 73, 9 C.F.R. 121, and 7 C.F.R. 331)
 - Effective February 7, 2003
- Final Rule: “Possession, Use, and Transfer of Select Agents and Toxins” (42 C.F.R. 73, 9 C.F.R. 121, and 7 C.F.R. 331)
 - Effective April 18, 2005
- Interim Final Rule: “Reconstructed Replication Competent Forms of the 1918 Pandemic Influenza Virus Containing Any Portion of the Coding Regions of All Eight Gene Segments” (42 C.F.R. 73)
 - Effective October 20, 2005

How the Select Agent List Was Established

- April 22, 2002 - Interagency workgroup established
 - List of agents, security, toxins, exemptions, & rDNA
- June 12, 2002 - Public Health Security and Bioterrorism Preparedness and Response Act
- June 17, 2002 - 13 Professional organizations invited to speak to Interagency workgroup
- Aug. 23, 2002 - Published revised list for comment
- Dec. 13, 2002 - Published Interim Final Rule
- Feb. 11, 2003 – Comments due (111 received)
- March 18, 2005 – Published Final Rule

Intragovernmental Select Agents & Toxins Technical Advisory Committee

- Originated in 2002 by HHS
 - SME's from 21 Federal entities
- Currently Co-Chaired by HHS and USDA
 - HHS (CDC, NIH, FDA), USDA (APHIS, ARS, CVB), DOD
- Provide technical review & recommendations to CDC & APHIS Select Agent Programs on:
 - List of agents
 - Requests for exclusion of an attenuated strain
 - Review restricted experiment requests



Types of Select Agents and Toxins

- **HHS-only Agents** (HHS has sole authority and responsibility to regulate), n= 21
 - Select agents and toxins that may affect public health and safety
- **USDA-only Agents** (USDA has sole authority and responsibility to regulate), n=31
 - Select agents and toxins that may affect animal and plant health and animal and plant products
- **“Overlap Agents,”** n=20
 - Select agents and toxins subject to regulation by both agencies (~90%)



Genetic Elements, Recombinant Nucleic Acids, And Recombinant Organisms

(Sections 3 & 4 (c))

- 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 any toxins listed if the nucleic acids:
 - (i) can be expressed in vivo or in vitro, or
 - (ii) 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.



CDC

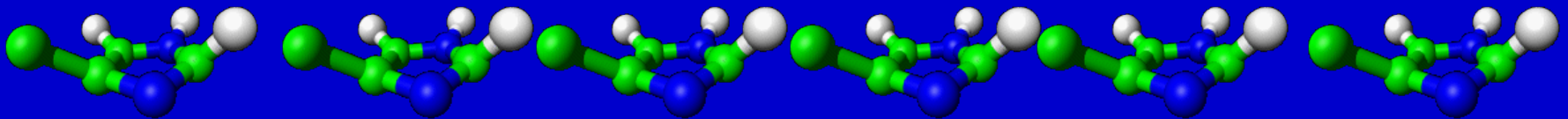
Rationale

- Based on the criteria set forth in the Act
 - Effect of exposure
 - Degree of contagiousness or pathogenicity
- Regulate those nucleic acids that are in a form that can cause disease (virulence factor):
 - *Viruses – Ability to produce more virus*
 - *Bacteria – Ability to express a functional toxin*
- Excludes (other than those listed above):
 - *Whole genomic material*
 - *Partial genomes*

Synthetic Genomics and the Select Agent Rules

Subject to the select agent rules:

- Nucleic acids (synthetic or naturally derived) that encode for a select agent virus that are intrinsically infectious.
 - + *single-stranded RNA viruses (e.g., EEE, VEE, TBE)*
 - *Double-stranded DNA virus (Herpes B virus)*
- Any select agent created from nucleic acids (synthetic or naturally derived).
 - i.e., 1918 influenza virus



Not subject to the select agent rules:

- Nucleic acids (synthetic or naturally derived) that encode for other select agent viruses, bacteria, or fungi because these nucleic acids are not intrinsically infectious or replication-competent.

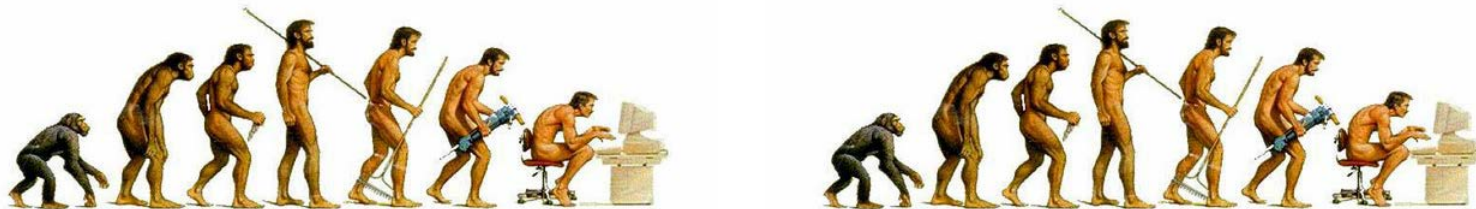


Synthetic Genomics and the Select Agent Rules (Toxins)

- Subject to the select agent rules:
 - Recombinant nucleic acids that encode for, and can express, a functional select agent toxin.
- Not subject to the select agent rules:
 - Nucleic acids that encode for individual subunits that are not toxic.

Evolution of the Regulatory Language for Select Agent Nucleotides

- “Factor associated with a disease” or “Virulence factor sufficient to cause disease”
- “Full length nucleic acids”
 - Number of nucleotides or percent of genome
- “Nucleic acid sequences coding for any of the toxins, or their toxic subunits”



- 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 any toxins listed if the nucleic acids:
 - (i) can be expressed in vivo or in vitro, or
 - (ii) are in a vector or recombinant host genome and can be expressed in vivo or in vitro.

Summary

- **The SAR represent a balance of regulatory oversight with realistic impacts on scientific community in order to minimize disruption or termination of legitimate research, educational, or biodefense-related projects**
- **Regulatory oversight has flexibility to respond promptly to public or agricultural health threats**
 - **Addition of 1918 influenza to HHS list**
- **However, synthetic genomics (like traditional rDNA techniques) has the potential to produce novel agents that defy current taxonomic classification**
- **Development of recommendations from NSABB important in assisting the government to address this complex issue**