

Federal Select Agent Program Perspective:

*Intersection of the NIH Guidelines with the
Select Agent Regulations*

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NIH Guidelines: Honoring the Past, Charting the Future



July 18, 2017

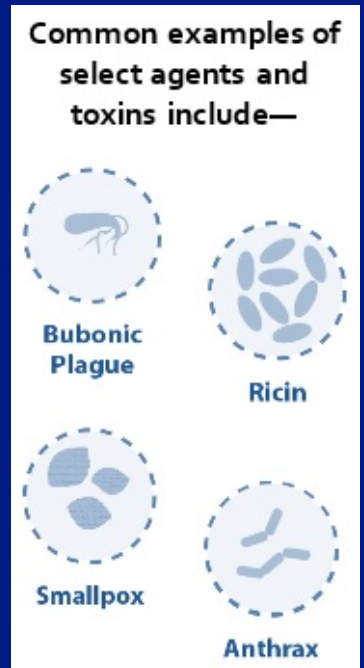


Federal Select Agent Program (FSAP)

- ❑ FSAP regulates the possession, use, and transfer of biological select agents and toxins that have the potential to pose a severe threat to public, animal or plant health, or to animal or plant products

- ❑ **Managed jointly by:**

- The Division of Select Agents and Toxins (DSAT) at the Centers for Disease Control and Prevention (CDC), part of the U.S. Department of Health and Human Services (HHS)
- The Agriculture Select Agent Services (AgSAS) at the Animal and Plant Health Inspection Service (APHIS), part of the U.S. Department of Agriculture (USDA)



FSAP: Background

- ❑ DSAT regulates agents that cause disease in humans
- ❑ AgSAS regulates agents that cause disease in animals or plants
- ❑ Share the responsibility for agents that threaten both humans and animals



Key Regulatory Functions & Activities

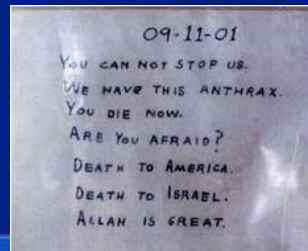
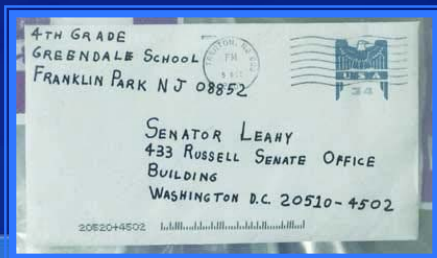
- ❑ **Promulgate the select agent regulations**
 - 7 C.F.R. Part 331; 9 C.F.R. Part 121; 42 C.F.R. Part 73
- ❑ **Provide oversight of possession, use, and transfer**
- ❑ **Conduct inspections and approve registrations**
- ❑ **Approve individual access to select agents & toxins**
- ❑ **Receive reports of a theft, loss, or release**
- ❑ **Take appropriate enforcement actions**
- ❑ **Serve as a resource on compliance with the regulations**

	BACKLOG FORM TO REPORT POTENTIAL HAZARD, L1, L2, L3, L4, L5, L6, L7, L8, L9, L10, L11, L12, L13, L14, L15, L16, L17, L18, L19, L20, L21, L22, L23, L24, L25, L26, L27, L28, L29, L30, L31, L32, L33, L34, L35, L36, L37, L38, L39, L40, L41, L42, L43, L44, L45, L46, L47, L48, L49, L50, L51, L52, L53, L54, L55, L56, L57, L58, L59, L60, L61, L62, L63, L64, L65, L66, L67, L68, L69, L70, L71, L72, L73, L74, L75, L76, L77, L78, L79, L80, L81, L82, L83, L84, L85, L86, L87, L88, L89, L90, L91, L92, L93, L94, L95, L96, L97, L98, L99, L100, L101, L102, L103, L104, L105, L106, L107, L108, L109, L110, L111, L112, L113, L114, L115, L116, L117, L118, L119, L120, L121, L122, L123, L124, L125, L126, L127, L128, L129, L130, L131, L132, L133, L134, L135, L136, L137, L138, L139, L140, L141, L142, L143, L144, L145, L146, L147, L148, L149, L150, L151, L152, L153, L154, L155, L156, L157, L158, L159, L160, L161, L162, L163, L164, L165, L166, L167, L168, L169, L170, L171, L172, L173, L174, L175, L176, L177, L178, L179, L180, L181, L182, L183, L184, L185, L186, L187, L188, L189, L190, L191, L192, L193, L194, L195, L196, L197, L198, L199, L200, L201, L202, L203, L204, L205, L206, L207, L208, L209, L210, L211, L212, L213, L214, L215, L216, L217, L218, L219, L220, L221, L222, L223, L224, L225, L226, L227, L228, L229, L230, L231, L232, L233, L234, L235, L236, L237, L238, L239, L240, L241, L242, L243, L244, L245, L246, L247, L248, L249, L250, L251, L252, L253, L254, L255, L256, L257, L258, L259, L260, L261, L262, L263, L264, L265, L266, L267, L268, L269, L270, L271, L272, L273, L274, L275, L276, L277, L278, L279, L280, L281, L282, L283, L284, L285, L286, L287, L288, L289, L290, L291, L292, L293, L294, L295, L296, L297, L298, L299, L300, L301, L302, L303, L304, L305, L306, L307, L308, L309, L310, L311, L312, L313, L314, L315, L316, L317, L318, L319, L320, L321, L322, L323, L324, L325, L326, L327, L328, L329, L330, L331, L332, L333, L334, L335, L336, L337, L338, L339, L340, L341, L342, L343, L344, L345, L346, L347, L348, L349, L350, L351, L352, L353, L354, L355, L356, L357, L358, L359, L360, L361, L362, L363, L364, L365, L366, L367, L368, L369, L370, L371, L372, L373, L374, L375, L376, L377, L378, L379, L380, L381, L382, L383, L384, L385, L386, L387, L388, L389, L390, L391, L392, L393, L394, L395, L396, L397, L398, L399, L400, L401, L402, L403, L404, L405, L406, L407, L408, L409, L410, L411, L412, L413, L414, L415, L416, L417, L418, L419, L420, L421, L422, L423, L424, L425, L426, L427, L428, L429, L430, L431, L432, L433, L434, L435, L436, L437, L438, L439, L440, L441, L442, L443, L444, L445, L446, L447, L448, L449, L450, L451, L452, L453, L454, L455, L456, L457, L458, L459, L460, L461, L462, L463, L464, L465, L466, L467, L468, L469, L470, L471, L472, L473, L474, L475, L476, L477, L478, L479, L480, L481, L482, L483, L484, L485, L486, L487, L488, L489, L490, L491, L492, L493, L494, L495, L496, L497, L498, L499, L500, L501, L502, L503, L504, L505, L506, L507, L508, L509, L510, L511, L512, L513, L514, L515, L516, L517, L518, L519, L520, L521, L522, L523, L524, L525, L526, L527, L528, L529, L530, L531, L532, L533, L534, L535, L536, L537, L538, L539, L540, L541, L542, L543, L544, L545, L546, L547, L548, L549, L550, L551, L552, L553, L554, L555, L556, L557, L558, L559, L560, L561, L562, L563, L564, L565, L566, L567, L568, L569, L570, L571, L572, L573, L574, L575, L576, L577, L578, L579, L580, L581, L582, L583, L584, L585, L586, L587, L588, L589, L590, L591, L592, L593, L594, L595, L596, L597, L598, L599, L600, L601, L602, L603, L604, L605, L606, L607, L608, L609, L610, L611, L612, L613, L614, L615, L616, L617, L618, L619, L620, L621, L622, L623, L624, L625, L626, L627, L628, L629, L630, L631, L632, L633, L634, L635, L636, L637, L638, L639, L640, L641, L642, L643, L644, L645, L646, L647, L648, L649, L650, L651, L652, L653, L654, L655, L656, L657, L658, L659, L660, L661, L662, L663, L664, L665, L666, L667, L668, L669, L670, L671, L672, L673, L674, L675, L676, L677, L678, L679, L680, L681, L682, L683, L684, L685, L686, L687, L688, L689, L690, L691, L692, L693, L694, L695, L696, L697, L698, L699, L700, L701, L702, L703, L704, L705, L706, L707, L708, L709, L710, L711, L712, L713, L714, L715, L716, L717, L718, L719, L720, L721, L722, L723, L724, L725, L726, L727, L728, L729, L730, L731, L732, L733, L734, L735, L736, L737, L738, L739, L740, L741, L742, L743, L744, L745, L746, L747, L748, L749, L750, L751, L752, L753, L754, L755, L756, L757, L758, L759, L760, L761, L762, L763, L764, L765, L766, L767, L768, L769, L770, L771, L772, L773, L774, L775, L776, L777, L778, L779, L780, L781, L782, L783, L784, L785, L786, L787, L788, L789, L790, L791, L792, L793, L794, L795, L796, L797, L798, L799, L800, L801, L802, L803, L804, L805, L806, L807, L808, L809, L810, L811, L812, L813, L814, L815, L816, L817, L818, L819, L820, L821	
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Overview & History

- ❑ 2001 anthrax attacks led to strengthening of program
- ❑ Title II of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002
 - Led to creation of the current Federal Select Agent Program
 - Increased safeguards and security measures for select agents
 - Strengthened the regulatory authorities of HHS
 - Granted comparable regulatory authorities to USDA
- ❑ List-based regulatory program (currently 66 agents)
- ❑ Requires republication of agent list every two years



TITLE II—ENHANCING CONTROLS ON DANGEROUS BIOLOGICAL AGENTS AND TOXINS

“SEC. 351A. ENHANCED CONTROL OF DANGEROUS BIOLOGICAL AGENTS AND TOXINS.

“(a) REGULATORY CONTROL OF CERTAIN BIOLOGICAL AGENTS AND TOXINS.—

“(1) LIST OF BIOLOGICAL AGENTS AND TOXINS.—

“(A) IN GENERAL.—The Secretary shall by regulation establish and maintain a list of each biological agent and each toxin that has the potential to pose a severe threat to public health and safety.

“(B) CRITERIA.—In determining whether to include an agent or toxin on the list under subparagraph (A), the Secretary shall—

“(i) consider—

“(I) the effect on human health of exposure to the agent or toxin;

“(II) the degree of contagiousness of the agent or toxin and the methods by which the agent or toxin is transferred to humans;

“(III) the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent any illness resulting from infection by the agent or toxin; and

“(IV) any other criteria, including the needs of children and other vulnerable populations, that the Secretary considers appropriate; and

“(ii) consult with appropriate Federal departments and agencies and with scientific experts representing appropriate professional groups, including groups with pediatric expertise.

“(2) BIENNIAL REVIEW.—The Secretary shall review and republish the list under paragraph (1) biennially, or more often as needed, and shall by regulation revise the list as necessary in accordance with such paragraph.

TITLE II—ENHANCING CONTROLS ON DANGEROUS BIOLOGICAL AGENTS AND TOXINS

SEC. 211. SHORT TITLE.

This subtitle may be cited as the “Agricultural Bioterrorism Protection Act of 2002”.

SEC. 212. REGULATION OF CERTAIN BIOLOGICAL AGENTS AND TOXINS.

(a) REGULATORY CONTROL OF CERTAIN BIOLOGICAL AGENTS AND TOXINS.—

(1) LIST OF BIOLOGICAL AGENTS AND TOXINS.—

(A) IN GENERAL.—The Secretary of Agriculture shall by regulation establish and maintain a list of each biological agent and each toxin that the Secretary determines has the potential to pose a severe threat to animal or plant health, or to animal or plant products.

(B) CRITERIA.—In determining whether to include an agent or toxin on the list under subparagraph (A), the Secretary shall—

(i) consider—

(I) the effect of exposure to the agent or toxin on animal or plant health, and on the production and marketability of animal or plant products;

(II) the pathogenicity of the agent or the toxicity of the toxin and the methods by which the agent or toxin is transferred to animals or plants;

(III) the availability and effectiveness of pharmacotherapies and prophylaxis to treat and prevent any illness caused by the agent or toxin; and

(IV) any other criteria that the Secretary considers appropriate to protect animal or plant health, or animal or plant products; and

(ii) consult with appropriate Federal departments and agencies and with scientific experts representing appropriate professional groups.

(2) BIENNIAL REVIEW.—The Secretary shall review and republish the list under paragraph (1) biennially, or more often as needed, and shall by regulation revise the list as necessary in accordance with such paragraph.

Select Agent Regulations

- ❑ Take into consideration the national biosafety standards – including *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*, NIH guidelines
- ❑ Other sources drawn from:
 - ISATTAC*, Ag-ISATTAC, public comment
 - Agricultural standards – including the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, the USDA Agricultural Research Service (ARS) *Facilities Design Standards*, and the United States Animal Health Association *Foreign Animal Diseases*

* *Intragovernmental Select Agents and Toxins Technical Advisory Committee*

Select Agent Regulations

- ❑ **Restricted experiments language taken from NIH guidelines**
 - Set of very specific experiments that require pre-approval
 - NIH defers to FSAP on requests to conduct a restricted experiment with select agents
 - NIH guidelines are not federal regulations and are limited to research supported by federal funding



Section III-A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation (See [Section IV-C-1-b-\(1\)](#), Major Actions).

Section III-A-1. Major Actions under the NIH Guidelines

Experiments considered as *Major Actions* under the *NIH Guidelines* cannot be initiated without submission of relevant information on the proposed experiment to the Office of Science Policy, National Institutes of Health, preferably by e-mail to: NIHGuidelines@od.nih.gov, the publication of the proposal in the *Federal Register* for 15 days of comment, review by RAC, and specific approval by NIH. The containment conditions or stipulation requirements for such experiments will be recommended by RAC and set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in [Appendix D, Major Actions Taken under the NIH Guidelines](#), which may be obtained from the Office of Science Policy, National Institutes of Health, preferably by submitting a request for this information to: NIHGuidelines@od.nih.gov; additional contact information is also available [here](#) and on the [OSP website](http://www.osp.od.nih.gov) (www.osp.od.nih.gov).

Section III-A-1-a. 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 ability to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by the RAC.

**NIH Guidelines for
Research Involving
Recombinant or
Synthetic Nucleic
Acid Molecules
April 2016**

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Section III-B. Experiments That Require NIH OSP and Institutional Biosafety Committee Approval Before Initiation

Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH OSP. The containment conditions for such experiments will be determined by NIH OSP in consultation with *ad hoc* experts. Such experiments require Institutional Biosafety Committee approval before initiation (see [Section IV-B-2-b-\(1\)](#), *Institutional Biosafety Committee*).

Section III-B-1. Experiments Involving the Cloning of Toxin Molecules with LD₅₀ of Less than 100 Nanograms per Kilogram Body Weight

Deliberate formation of recombinant or synthetic nucleic acid molecules containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD₅₀ of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and *Shigella dysenteriae* neurotoxin). Specific approval has been given for the cloning in *Escherichia coli* K-12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Specific experiments already approved under this section may be obtained from the Office of Science Policy, National Institutes of Health, preferably by submitting a request for this information to: NIHGuidelines@od.nih.gov; additional contact information is also available [here](#) and on the [OSP website](http://www.osp.od.nih.gov) (www.osp.od.nih.gov).

Select Agent Regulations: Restricted Experiments

§73.13 Restricted experiments.

(a) An individual or entity may not conduct, or possess products resulting from, the following experiments unless approved by and conducted in accordance with the conditions prescribed by the HHS Secretary:

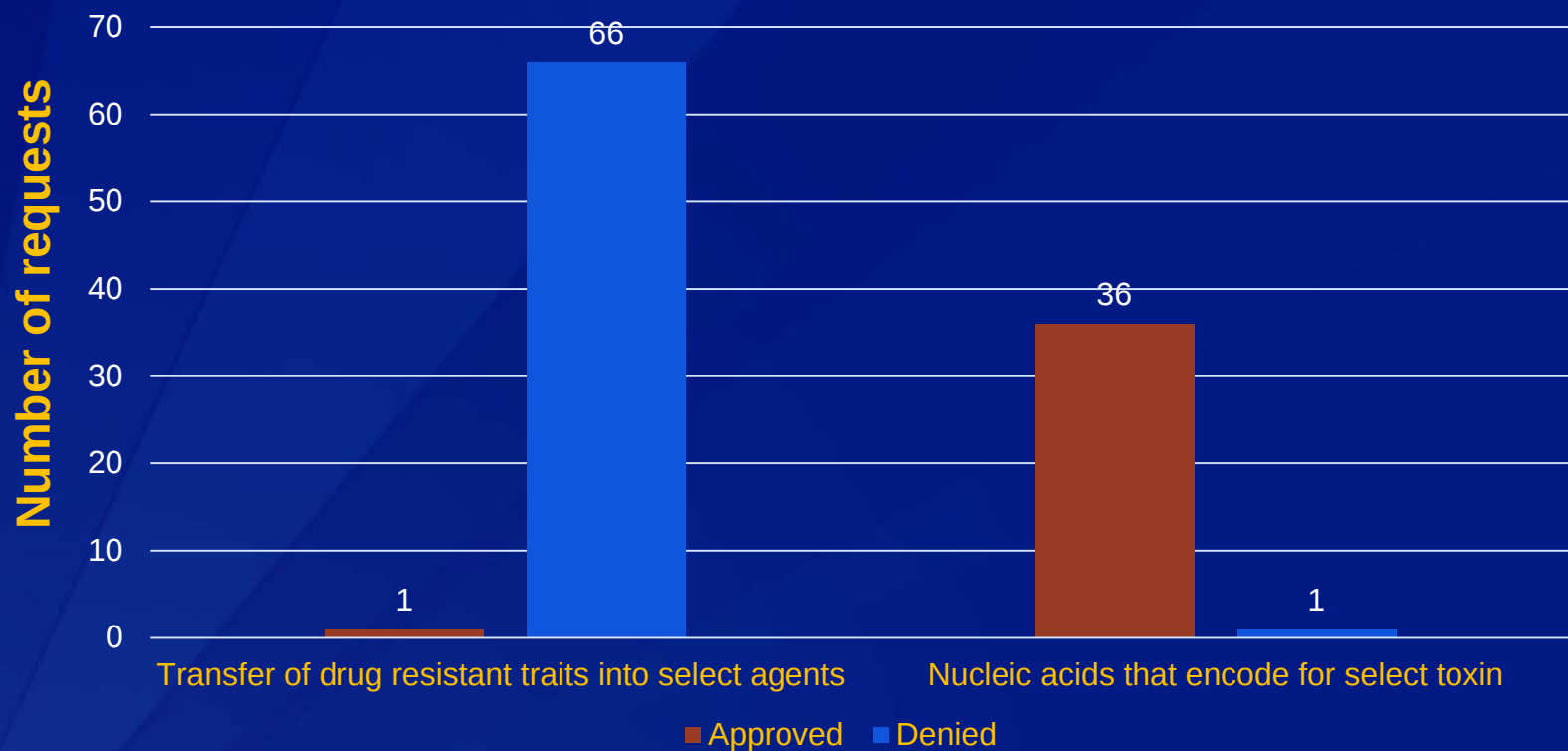
(1) Experiments that involve the deliberate transfer of, or selection for, a drug resistance trait to select agents that are not known to acquire the trait naturally, if such acquisition could compromise the control of disease agents in humans, veterinary medicine, or agriculture.

(2) Experiments involving the deliberate formation of synthetic or recombinant DNA containing genes for the biosynthesis of select toxins lethal for vertebrates at an LD₅₀ <100 ng/kg body weight.

42 CFR §73.13: Must be approved by the HHS Secretary

7 CFR §331.13, 9 CFR §121.13: Must be approved by the APHIS Administrator

Restricted experiments approved and denied by experiment type, 2006-2017 (DSAT)



Sources: 1). Smith J, Gangadharan D, Weyant R. Review of Restricted Experiment Requests, Division of Select Agents and Toxins, Centers for Disease Control and Prevention, 2006-2013. *Health Security* 2015;13:207-316; 2). Unpublished data

Conclusions

- ❑ FSAP approval for use of a select agent or toxin under the select agent regulations is, with the exception of “restricted experiments,” limited to consideration of whether the use can be done safely and securely.
- ❑ The consideration of whether a use should be allowed based on whether the results may have “dual-use” or “gain of function” implications is beyond the scope of the current Federal Select Agent Regulations.
- ❑ FSAP does not regulate information produced from select agent and toxin experiments.

Current Challenges

- ❑ List-based regulatory authority does not capture *de novo* created agents
- ❑ US Government policies controlled by federal funding:
 - Dual-use research of concern (DURC), or
 - Gain of function (GOF)
 - Specific to certain agents and toxins
 - Experiments listed in very broad terms
- ❑ NIH guidelines – involve Principal Investigator and Institutional Biosafety Committee (IBC); not the Responsible Official
 - Chimeric select agents
 - Theft/loss/release (TLR) reports on regulated nucleic acids

Discussion

www.selectagents.gov

CDC: lsat@cdc.gov or 404-718-2000

APHIS: AqSAS@aphis.usda.gov or
301-851-3300 option 3 (voice only)

