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Review of Requests to Exclude Attenuated Strains of Select Agents and Modified Select Toxins, Division of Select Agents and Toxins, Centers for Disease Control and Prevention, 2003–2017

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Abstract

The Centers for Disease Control and Prevention's Division of Select Agents and Toxins (DSAT) regulates the possession, use, and transfer of select agents and toxins throughout the United States as part of the Federal Select Agent Program. The Department of Health and Human Services (HHS) select agent regulations also include criteria for the exclusion of select agents and toxins from the requirements of the regulations (42 CFR § 73.3 and 73.4). An entity may request the exclusion of an attenuated strain of a select agent or a select toxin modified to be less potent or toxic. The Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC) reviews the exclusion request by conducting a risk assessment to determine whether the attenuated strain or modified toxin has the potential to pose a severe risk to public health and safety. In this study, DSAT analyzed the number and types of exclusion requests reviewed by the ISATTAC from January 2003 through December 2017. As of December 2017, DSAT has excluded 50 strains of biological agents and 10 modified toxins from the select agent regulations. The select agent regulations provision for the exclusion of attenuated select agents or modified toxins that no longer have the potential to pose a severe threat to public health and safety is an important mechanism for reducing the regulatory burden on entities that do not need to work with the fully virulent or toxic forms of the agent or toxin. This provision may have the added benefit of encouraging entities to consider working with variants of select agents or toxins that are of less risk than the fully virulent or toxic forms in their research studies and as a positive control.

Keywords

Select agents; Public health preparedness/response; Biosafety

The Public Health and Bioterrorism Preparedness and Response Act of 2002 (42 U.S.C. 262a) (also known as the Bioterrorism Act of 2002) requires the Department of Health and Human Services (HHS) Secretary and the US Department of Agriculture (USDA) Secretary

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to publish regulations to strengthen oversight of biological select agents and toxins (BSATs) that have the potential to pose a severe threat to public health, animal and plant health, or animal and plant products. The regulated BSATs are referred to as select agents and toxins. Common examples of select agents and toxins include the organisms that cause anthrax, smallpox, bubonic plague, foot-and-mouth disease, avian influenza, classical swine fever, bacterial blight, and botulism.

The Bioterrorism Act also requires that the HHS Secretary and the USDA Secretary review and republish the list of select agents and toxins on at least a biennial basis. The Federal Select Agent Program will seek public comment via a *Federal Register* notice with recommendations to add or remove specific BSATs or exclude a subset of BSAT strains or serotypes from the select agent list. The final determination is made by the HHS Secretary and USDA Secretary with the publication of a final rule.

The Centers for Disease Control and Prevention's (CDC) Division of Select Agents and Toxins (DSAT) regulates the possession, use, and transfer of select agents and toxins that have been identified as having the potential to pose a severe threat to public health and safety. In determining whether to regulate an agent or toxin that poses a severe threat to public health, DSAT considers the effect on human health of exposure to an agent or toxin; the degree of contagiousness of the agent or toxin; the methods by which the agent or toxin is transferred to humans; the availability and effectiveness of pharmacotherapies and immunizations to treat and prevent illnesses resulting from an agent or toxin; the potential for an agent or toxin to be used as a biological weapon; and the needs of children and other vulnerable populations.

DSAT provides regulatory oversight for select agents and toxins that cause disease in humans (also known as "HHS-only" agents) and zoonotic agents (also known as "overlap agents") (42 CFR 73).[1] Overlap agents are also regulated by the USDA (9 CFR 121.4). DSAT currently regulates 46 HHS and overlap select agents and toxins (a complete list of regulated select agents and toxins can be found on the select agent website).[2] Of these, 12 are considered Tier 1 select agents and toxins. Tier 1 agents have the potential to pose the greatest risk of deliberate misuse with significant potential for mass casualties or devastating effects to the economy, critical infrastructure, and/or public confidence. In some cases, a biological agent can be attenuated or a biological toxin can be modified such that they do not have the potential to pose a severe threat to public health and safety.

The select agent regulations contain provisions that allow the Federal Select Agent Program to exclude select agents and toxins from the requirements of the select agent regulations. One of the exclusion provisions allows an entity to submit a written request to the program asking that an attenuated strain of a select agent or a select toxin modified to be less potent or toxic be excluded from the requirements of the select agent regulations. The request must contain the rationale and scientific references and/or supporting documentation that demonstrate the attenuated strain or modified toxin does not have the potential to pose a severe threat to public health and safety.

As part of its evaluation process, DSAT seeks technical advice and scientific input from CDC's Intragovernmental Select Agents and Toxins Technical Advisory Committee (ISATTAC) to review exclusion requests. The ISATTAC is composed of federal government employees from CDC, the National Institutes of Health (NIH), the Food and Drug Administration (FDA), the USDA Animal and Plant Health Inspection Service (APHIS), the USDA Agricultural Research Service (ARS), the USDA Center for Veterinary Biologics (CVB), the Department of Homeland Security (DHS), and the Department of Defense (DOD). The ISATTAC provides the DSAT director with a recommendation on whether the exclusion should be granted, denied, or deferred until the requestor provides further information. If the recommendation pertains to an overlap agent, then the concurrence of Agriculture Select Agent Services (AgSAS) is required. If the DSAT director denies an exclusion request for an HHS-only agent, the entity has the right to appeal the decision by providing additional data or supporting information for review [42 C.F.R § 73.3 (e)(3) and 42 C.F.R § 73.4 (e)(3)]. If the DSAT director, with the concurrence of AgSAS, if applicable, grants an exclusion request for an HHS-only or overlap agent, the requestor is notified of the effective date of the exclusion and the information is posted publicly on the select agent website (www.selectagents.gov). The ISATTAC's recommendations are considered by both the DSAT and AgSAS director for overlap agents.

If an excluded attenuated strain or modified toxin is subjected to any manipulation that restores or enhances its virulence or toxic activity, the resulting biological agent or toxin will again be subject to the select agent regulations. This article describes the number and types of exclusion requests DSAT has reviewed and the decisions rendered from January 2003 to December 2017.

MATERIALS AND METHODS

DSAT and the ISATTAC conducted risk assessments for each exclusion request to determine if the attenuated select agent strain or modified toxin had the potential to pose a severe risk to public health and safety. The risk assessment criteria used to evaluate whether a strain or toxin should be excluded from the select agent regulations during the study period were defined by the ISATTAC as follows:

- Documented history of not causing severe disease in humans or relevant animal models and therefore does not pose a risk to public health and safety. To meet this criterion, an entity provides attenuation data comparing the newly attenuated select agent strain with an avirulent non–select agent from the same genus, demonstrating that the attenuated select agent did not have the potential to pose a greater risk than the similar non–select agent. For example, *Burkholderia pseudomallei* capsule cluster mutant strain JW270 was shown to be attenuated by ~5 log reduction to the level of avirulent *B. thailandensis* (a non–select agent) in a hamster animal model.[3]
- Defined genetic mutations or alterations known to attenuate virulence or toxicity in humans or relevant animal models. For example, all *Yersinia pestis* strains that lack the 75 kb low-calcium response (Lcr) virulence plasmid are excluded because strains lacking this plasmid (Lcr^-) are irreversibly attenuated.

- Data showing the mutations had a very low frequency of reversion to wild-type virulence or toxicity. For example, Botulinum neurotoxin type C atoxic derivatives contain mutations in 3 original amino acids (E446; H449; Y591), thus making it difficult for reversion to wild-type toxin.
- Level of difficulty in engineering the attenuated strain or modified toxin to restore wild-type virulence or toxicity.
- Quantitative measures demonstrating a change in virulence or reduction in toxicity in an appropriate animal model. For each pathogen, the sample size and type of animal model used to test virulence or toxicity was considered for exclusion determination. For example, *Yersinia pestis* CO92 triple mutant Δ*lpp*Δ*msbB*Δ*ail* studies demonstrated that the triple mutant is significantly attenuated (100% animal survival in a pneumonic plague mouse model) at high infectious doses [2.0–3.4 × 10^6 colony-forming units (CFU)], which is equivalent to a 4,000–6,800 lethal dose to kill 50% of mice (LD_{50}) by the wild-type Y. *pestis* CO92 strain.[4]
- Information regarding tests that might have been conducted to differentiate animals exposed to the attenuated strain from those infected with the wild-type organism. For example, the Δ*norD*, Δ*znuA Brucella melitensis*-lacZ strain contains the deletion of 2 virulence genes and the addition of the *E.coli lacZ* marker gene to differentiate between the Δ*norD*, Δ*znuA Brucella melitensis*-lacZ strain and wild-type *B. melitensis*.[5]
- Related published scientific papers that support the methods and data provided for the exclusion. For example, *B. pseudomallei* strain 576mn is a Δ*purM* derivative of the wild-type strain 576a. Norris et al demonstrated that strain 576mn was auxotrophic for adenine in minimal media, unable to replicate in human cells, significantly attenuated in BALB/C mice studies following high-dose intranasal inoculation (100% animal survival), and significantly attenuated compared to wild-type *B. pseudomallei* 576a strain.[6]

The ISATTAC reviewed each exclusion request and recommended whether to grant or deny the request or defer a decision until the requestor provided additional information. The ISATTAC's recommendation was considered by the DSAT director for HHS-only agents and both the DSAT and AgSAS directors for overlap agents before a final determination was made. After all requested information was reviewed, a written decision granting or denying the request was issued to the applicant. The final decision for each exclusion request was recorded in an Excel database.

For this analysis, DSAT analyzed the number, decisions rendered, and types of exclusion requests received from January 2003 to December 2017 for HHS-only select agents and toxins and overlap select agents. Select agents that are regulated by the USDA only (ie, VS select agents and toxins listed under 7 CFR 331.3 and 9 CFR 121.3) were not included in this study. The following variables were abstracted from a DSAT database: entity type submitting the request (academic, non–federal government, federal government,

commercial, and private nonprofit laboratories), date of request submission, select agent or toxin identified in the request, and final determination of the request (approved or denied).

RESULTS

DSAT received a total of 79 requests to exclude a select agent strain or modified toxin from the requirements of the select agent regulations from calendar years 2003 to 2017 (Figure 1). Of those, 76% (n = 60) of the total requests were approved to exclude the attenuated select agent strain or less potent toxin because the submitter had adequately demonstrated to DSAT that the strain or toxin no longer had the potential to pose a severe threat to public health and safety. However, 24% (n = 19) (Figure 2) of the requests were denied, based on failure to meet 1 or more of the risk assessment criteria used to evaluate exclusion requests as described in the materials and methods section. Insufficient attenuation or toxicity data were the most common risk assessment criteria cited that failed to qualify the agent or toxin for exclusion consideration. Registered academic institutions submitted 80% of all exclusion requests (data not shown), although academic institutions represent only 32% (75/238) of entities registered with DSAT as of December 31, 2017.

In 2017, DSAT reviewed 15 exclusion requests, the second largest number reviewed by DSAT in 1 year since 2003 (Figure 1). Thirteen of the 15 requests were for the exclusion of attenuated strains of *Burkholderia* spp with the same mutation (*asd* gene deletion) and all were approved (Table 1). One of the 15 requests was for the exclusion of a modified Botulinum neurotoxin (BoNT), but the request was denied due to insufficient toxicity data. The remaining request was for the exclusion of a *Burkholderia pseudomallei* strain 576mn and was approved.

Of the total requests, 80% (63/79) were for the exclusion of an attenuated select agent; 20% (16/79) were for the exclusion of a modified select toxin. Seventy-nine percent (50/63) of all requests to exclude attenuated select agents were approved; 63% (10/16) of modified select toxin exclusion requests were approved (Figure 2). All of the denied select toxin requests were due to insufficient toxicity data (eg, animal data not provided). Attenuated strains of *Francisella tularensis* (n = 7/63 or 11% of all select agent requests), *Brucella abortus* (n = 6/63 or 10% of all select agent requests), and *Burkholderia pseudomallei* (n = 18/63 or 29% of all select agent requests) were the most frequently requested select agents for exclusion (Figure 3). Botulinum neurotoxin (n = 7/16 or 44% of all select toxin requests) was the most frequently requested select toxin for exclusion (Figure 3).

As of December 2017, there are 8 HHS or overlap select agent bacteria, 8 HHS or overlap select agent viruses, and 4 HHS select toxins that have 1 or more strains or subtypes that are excluded from the requirements of the select agent regulations (Table 1). Therefore, 43% (20/46) of all current HHS and overlap select agents and toxins have 1 or more strains that are excluded from the select agent regulations. All of the Tier 1 agents from the overlap select agent list (ie, *B. anthracis, B. mallei, B. pseudomallei*) and 4 out of 9 Tier 1 agents and toxins from the HHS list have at least 1 strain or subtype that is excluded from the select agent regulations.

Exemption vs Exclusion

The 42 CFR § 72.6 rule stated that attenuated strains of select agents approved for human vaccination purposes by FDA or other recognized national or international organization would be exempt. Therefore, the requests that were previously exempt under 42 CFR § 72.6 were reviewed for their potential to pose a severe threat to public health and safety. The requests were determined to also meet the exclusion provisions under the 42 CFR § 73 rule and were excluded between February 7, 2002, and October 15, 2003.

DISCUSSION

During the period between 2003 and 2017, DSAT approved the majority of attenuated or modified BSAT exclusion requests submitted for review. Use of excluded select agents and toxins provides an opportunity for researchers to use less virulent strains and/or less potent toxins to facilitate select agent and toxin research and diagnostics development, which provides an opportunity for a broader range of investigators to work with these strains, as access to them is no longer limited by the regulations.

Currently, there are excluded strains or modified toxins for every Tier 1 HHS select agent or Tier 1 overlap select agent except for Marburg virus, Botulinum neurotoxin-producing species of *Clostridium, B. cereus* biovar *anthracis*, and variola viruses (Table 1). A current list of excluded HHS and overlap select agents and toxins can be found on the Federal Select Agent Program website.[7] Exclusions granted from the select agent regulations are permanent unless an excluded attenuated strain or modified toxin is subsequently subjected to any manipulation that restores or enhances its virulence or toxic activity. If this occurs, the resulting biological agent or toxin will again be subject to the select agent regulations.

Registered academic institutions submitted 80% of all exclusion requests, which suggests that many universities elect to work with excluded select agents and toxins as safer alternatives to wild-type select agents and toxins. Many of the excluded strains are also used in diagnostic work as a safer alternative.

In addtion to the mechanism for exclusion described above, there are other mechanisms for exclusion. HHS/ DSAT can exclude specific strains or subtypes of BSAT from the regulations through the biennial review of the select agent and toxin list required under the Bioterrorism Act of 2002.[8] Additionally, some select agents and toxins can be automatically excluded if certain provisions are met as outlined in 42 CFR Section 73.3 (d) and 73.4 (d). If these provisions are met, prior review to exclude the agent or toxin is not required from the federal select agent program. These provisions include the following:

- Any select agent or toxin that is in its naturally occurring environment, provided the select agent or toxin has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source. For example, ricin is produced in maturing seeds of the castor bean. Therefore, ricin in its naturally occuring environment (castor beans) is not subject to the requirements of the select agent regulations.
- Nonviable select agents or nontoxic toxins.*

- A select agent or toxin that has been subjected to decontamination or a destruction procedure when intended for waste disposal.
- A select agent or regulated nucleic acids that can produce infectious forms of any select agent virus that has been subjected to a validated inactivation procedure that is confirmed through a viability testing protocol or a procedure that removes all viable select agent cells, spores, or virus particles if the material is determined by the HHS Secretary to be effectively inactivated or effectively removed.
- South America genotypes of Eastern equine encephalitis virus (EEEV).
- Any subtypes of Venezuelan equine encephalitis virus (VEEV), except for subtypes IAB or IC.
- The West African clade of monkeypox virus.
- Except as required in 42 CFR §73.16(l), the aggregate amount of the toxin under the control of a principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor does not, at any time, exceed the following amounts: 1,000 mg of Abrin; 1 mg of Botulinum neurotoxins; 100 mg of Conotoxins (short, paralytic alpha conotoxins containing the following amino acid sequence $X_1CCX_2PACGX_3X_4X_5X6CX_7$); 10,000 mg of Diacetoxyscirpenol; 1,000 mg of ricin; 500 mg of Saxitoxin; 100 mg of Staphylococcal enterotoxins (subtypes A-E); 10,000 mg of T-2 toxin; or 500 mg of Tetrodotoxin.
- An HHS select toxin identified in an original food sample or clinical sample.
- Botulinum neurotoxin that is produced as a byproduct in the study of Botulinum neurotoxin–producing species of *Clostridium* so long as the toxin has not been intentionally cultivated, collected, purified, or otherwise extracted, and the material containing the toxin is rendered nontoxic and disposed of within 30 days of the initiation of the culture.

In conclusion, DSAT routinely reviews requests to exclude attenuated select agents or modified toxins that do not pose a severe threat to public health and safety. There are several exclusion provisions in the select agent regulations, including, but not limited to, nonviable and nonfunctional select agents and toxins, select agents or toxins in their naturally occuring environment, specific genotypes or subtypes of select agents and toxins, an animal inoculated with or exposed to a select toxin, and select toxins under the aggregate amount threshold. The exclusion provisions in the select agent regulations may reduce the regulatory burden on stakeholders who possess or work with select agents and toxins that do not pose a severe risk to public health and safety, which may encourage and facilitate research on many of these agents and toxins.

*"Nonviable" and "nontoxic" are similar terms that may be defined as the loss of biological activity. For a select agent, the term "nonviable" means that a select agent is no longer capable of growing, replicating, infecting, or causing disease. For regulated nucleic acids, the term "nonviable" means that the nucleic acids are no longer capable of producing infectious forms of a select virus or expression of a functional select toxin without further genetic manipulation. For a select toxin, the term "nontoxic" means a toxin is no longer capable of exerting its toxic effect. Additional guidance on these terms can be found in https://www.selectagents.gov/egd-changes.html and https://www.selectagents.gov/irg-intro.html.

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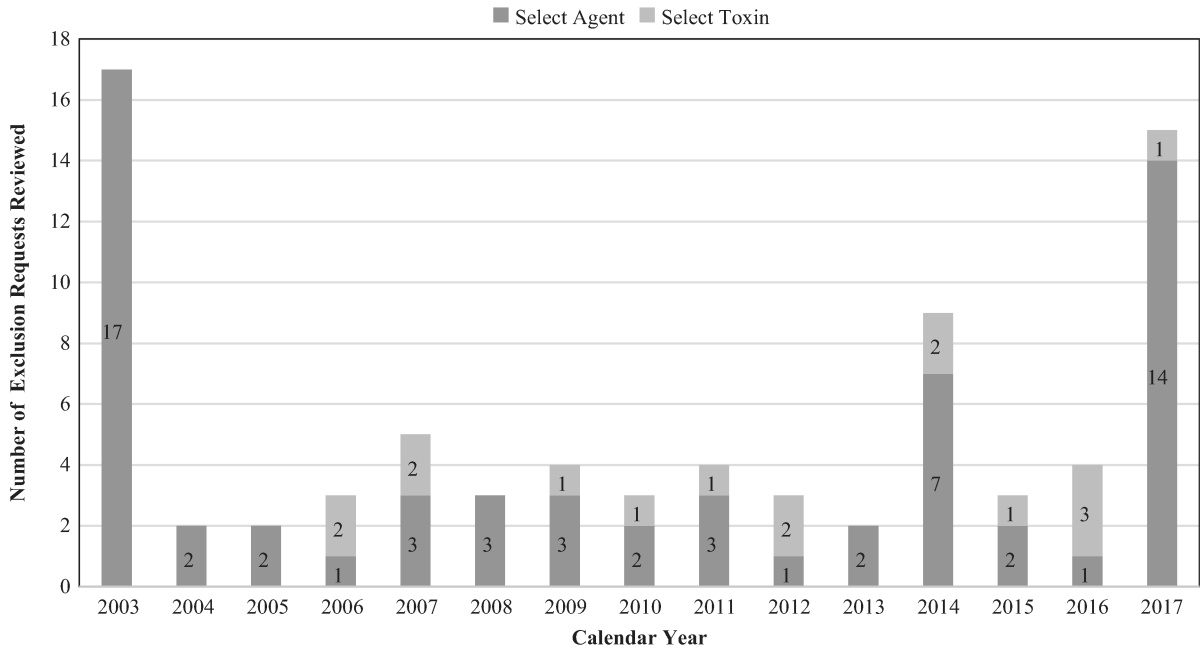

Figure 1.

Number of requests reviewed by DSAT to exclude an attenuated select agent or modified toxin from the select agent regulations, 2003 to 2017.

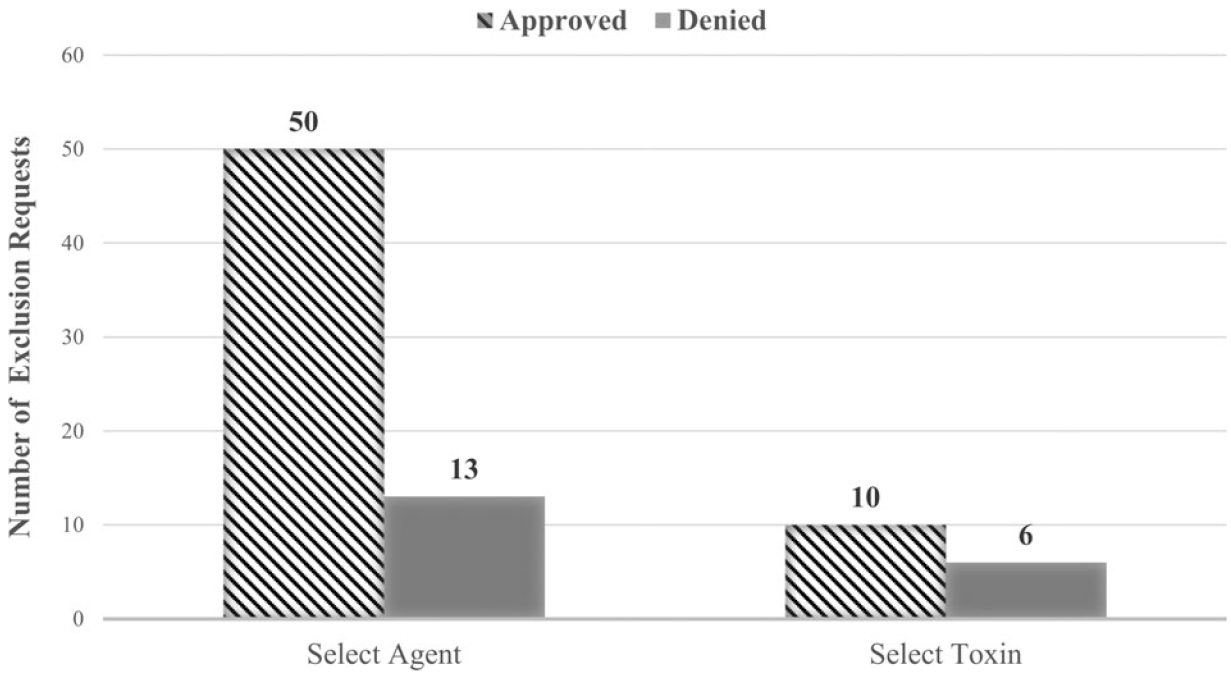

Figure 2.
Number of requests approved or denied by DSAT to exclude an attenuated select agent or modified toxin from the select agent regulations, 2003 to 2017.

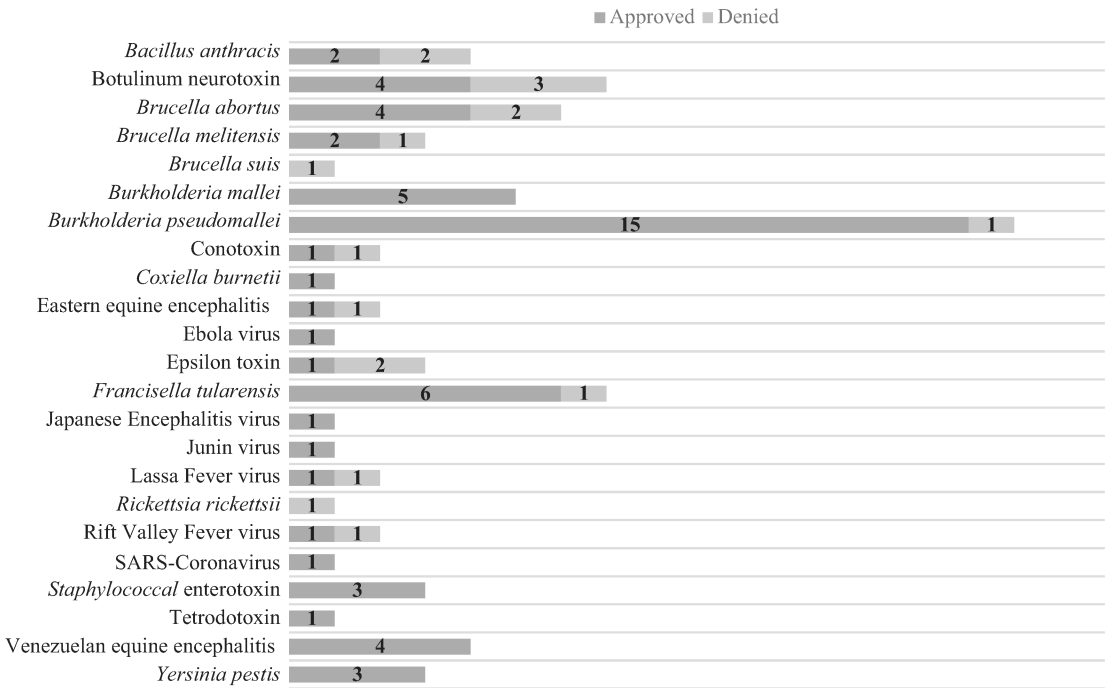

Figure 3.

Number of requests reviewed by DSAT to exclude an attenuated select agent or modified toxin from the select agent regulations by agent or toxin, 2003 to 2017.

Table 1.

List of Health and Human Services–only and overlap excluded attenuated select agents and modified select toxins (as of December 31, 2017)[a]

Agent or Toxin	Strain or Type	Exclusion Date
Bacillus anthracis[b]	Strains devoid of pX01 and pX02 Strains devoid of pX02 (Sterne)	02-27-2003 02-27-2003
Botulinum neurotoxin[b]	Catalytically inactive Botulinum neurotoxin (ciBoNT) B, C, E, F	03-23-2016
	Botulinum neurotoxin type C atoxic derivative (BoNT/C ad)	12-23-2014
	Fusion proteins of the heavy-chain domain of BoNT/translocation domain of diphtheria toxin	07-28-2011
	Recombinant catalytically inactive botulinum A1 holoprotein (ciBoNT/A1 HP)	05-07-2010
	BoNT/A1 atoxic derivative, ad, E224A/Y366A	07-22-2009
	Recombinant Botulinum neurotoxin serotype A (R362A, Y365F)	03-28-2006
Brucella abortus	Vaccine strain (ΔnorDΔznuA)	06-02-2011
	Vaccine strain S2308Δpgm	08-09-2006
	Vaccine strain 19	06-12-2003
	Vaccine strain RB51	05-07-2003
Brucella melitensis	ΔnorDΔznuA *B. melitensis*-lacZ 16MΔvjbR	07-07-2015 12-22-2014
Burkholderia mallei[b]	ATCC23344 Δ*asd*	12-13-2017
	Ivan Δ*asd*	12-13-2017
	China 5 Δ*asd*	12-13-2017
	2002721278 Δ*asd*	12-13-2017
	CHL001 (Δ*tonB* Δ*hcp1*)	08-20-2015
Burkholderia pseudomallei[b]	DL2 Δ*asd*	12-13-2017
	DL25 Δ*asd*	12-13-2017
	DL28 Δ*asd*	12-13-2017
	MSHR503 Δ*asd*	12-13-2017
	NAU44A6 Δ*asd*	12-13-2017
	MSHR840 Δ*asd*	12-13-2017
	MSHR 1655 Δ*asd*	12-13-2017
	MSHR87 Δ*asd*	12-13-2017

Agent or Toxin	Strain or Type	Exclusion Date
	MSHR367b Δ*asd*	12-13-2017
	576mn strain	08-18-2017
	K96243 Δ*asd*	04-24-2014
	MSHR487 Δ*asd*	04-24-2014
	capsular polysaccharide mutant strain, JW270	07-02-2014
	B0011 (a Δasd mutant of strain 1026b)	12-07-2011
	Bp82 (a ΔpurM mutant of strain 1026b)	04-14-2010
Conotoxins	non-short, paralytic alpha conotoxins	12-04-2012
Coxiella burnetii	Nine Mile Strain Phase II, plaque purified clone	10-15-2003
Eastern equine encephalitis virus	South American genotypes	12-04-2012
Ebola virus[b]	ΔVP30 replication incompetent virus	01-02-2013
Francisella tularensis[b] subsp. *novicida* and *Francisella novicida*-like strain	All strains of *Francisella tularensis* subsp. *novicida* and *Francisella novicida*-like strain	10-24-2014
	Utah 112 (ATCC 15482)	02-27-2003
Francisella tularensis[b] *subsp. tularensis*	SCHU S4ΔclpB strain B-38 (ATCC 6223)	11-10-2014
		02-27-2003
Francisella tularensis[b] subsp. *holarctica*	LVS (live vaccine strain) includes NDBR 101 lots, TSI-GSD lots, and ATCC 29684	02-27-2003
Junin virus	Vaccine strain Candid No. 1	02-07-2003
Lassa fever virus	Mopeia/Lassa arenavirus construct ML-29	03-02-2005
Monkeypox virus	West African clade	12-04-2012
Rift Valley fever virus	Vaccine candidate strain ΔNSs-ΔNSm-ZH501	03-12-2012
	Vaccine strain MP-12	02-07-2003
SARS-Coronavirus	NATtrol™ treated SARS-CoV molecular controls and RNA genomic material	02-08-2013
Staphylococcal enterotoxin	SEA single mutant (Q201A)	06-01-2016
	SEC single mutant (N23A)	06-01-2016
	SEA triple mutant (L48R, D70R, and Y92A)	01-16-2014
	SEB triple mutant (L45R, Y89A, Y94A)	01-16-2014
	SEC double mutant (N23A and Y94A)	01-16-2014
Tetrodotoxin	Anhydrotetrodoxin, a derivative of wild type tetrodotoxin	05-15-2015
Venezuelan equine encephalitis virus (VEEV)	Subtypes ID and IE	12-04-2012

Agent or Toxin	Strain or Type	Exclusion Date
	Vaccine candidate strain V3526	05-05-2003
	Vaccine strain TC-83	02-07-2003
Yersinia pestis[b]	ΔlppΔmsbBΔail CO92 strain	05-19-2016
	Pgm negative (Δpgm) (eg, EV76)	03-14-2003
	Lcr negative (eg, Tjiwidej S, CDC A1122)	02-27-2003

[a] A current list can be found on the select agent website (https://www.selectagents.gov).

[b] Denotes Tier 1 agents.

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