

## SELECT AGENT REGULATIONS (42 CFR 73)—SUMMARY AND PHASED-IN EFFECTIVE DATES

Entities conducting activities under existing 72.6 registration, or lawfully possessing agents, as of 2/7/03, are subject to 72.6 governing registration, until 11/12/03; developing security plans until 6/12/03; implementing security plans until 9/12/03; security training until 9/12/03; and transfer of agents/toxins until 3/12/03---then Part 73 supercedes Part 72. (42 CFR 73.0(a)) **The following phased-in effective dates apply to agents/toxins MIT lawfully has as of 2/7/03. [Feb. 7, 2003 is the effective date for all of Part 73, other than those effective dates shown in \*[brackets], for agents/toxins MIT grows, creates, or acquires after 2/7/03 (42 CFR 73.0(c))]:**

### 2/7/03 Effective Date ( 42 CFR 73.0(a)(1) and (2))

- **Definitions - 73.1**

- **Scope - 73.2:** Possession, use, transfer within US, and receipt from outside US of listed agents/toxins; export control laws govern exports of agents/toxins; DOT regulations govern transportation.

- **General Prohibition - 73.3:** Entities and Individuals may not possess, use or transfer within US or receive from outside US, Select Agents or Toxins, unless for a lawful purpose and in compliance with 42 CFR 73.

- **List of HHS Select Agents and Toxins (see attached) and Exclusions - 73.4:**

Volume-based exclusions per PI for toxins—Excluded are Up To:

- 100 mg. of Abrin/PI

- 100 mg. of Conotixin/PI

- 1,000 mg. of Diacetoxyscirpenol/PI

- 100 mg. of Ricin/PI

- 100 mg. of Saxitoxin/PI

- 100 mg. Shiga-like ribosome inactivating proteins/PI

- 100 mg. Tetrodotoxin/PI

- **List of Overlap (HHS and USDA) Select Agents and Toxins (see attached) and Exclusions - 73.5:**

Volume-based exclusions per PI for overlap toxins—Excluded are Up To:

- 0.5 mg. Botulinum neurotoxins/PI

- 5 mg. Staphylococcal enterotoxins/PI

- 100 mg. Clostridium perfringens epsilon toxin/PI

- 100 mg. Shigatoxin/PI

- 1,000 T-2 toxin/PI

Non-viable agent organisms/nonfunctional toxins also are excluded from HHS and Overlap lists.

- **Exemptions from Part 73 - 73.6:** For specimens only for diagnosis/proficiency/verification testing, but transfer provisions of 73.14 apply; agents/toxins regulated under and used in compliance with specified laws; and certain case by case exemptions granted by Secretary HHS.

- **Responsible Official (RO) - 73.9:** MIT Biosafety Officer, Dr. Claudia Mickelson; Richard Fink, Alternate RO.

- **Safety Plan and Implementation - 73.10:** Plan should consider biosafety standards for BL 2,3,4 labs in CDC's BMBL, except Appendix F, for agents; OSHA Lab Standard and Hazard Communication and BMBL Appendix I for toxins; and NIH Guidelines for Research Involving Recombinant DNA Molecules for genetic elements/recombinant nucleic acids/organisms; also RO must conduct and document regular, at least annual, inspections of compliance with Plan and confirm correction of identified deficiencies.

- **Emergency Response Plan and Implementation - 73.12:** Must meet OSHA's hazardous waste and emergency response standards; coordinate with Entity-wide plans and outside parties; address agent/toxin hazards, roles, training, communications, emergency prevention, safe distances/refuge, security, evacuation, decontamination, medical resources, review critique and follow-up, personal protective equipment, and other issues.

- **Training In Safety and Emergency Response - 73.13:** For all Individuals with access to agents/toxins who require 73.8 AG security risk approval and are not subject to OSHA Bloodborne Pathogen standard; and all Individuals not seeking AG approval, visiting or having escorted access (e.g., custodians and other non-lab activity workers) to areas where agents/toxins are handled or stored. Training required before work in areas where agent/toxins are present, prior to new exposures, and annually. RO may certify that Individual already

using agents/toxins has necessary knowledge in lieu of initial training only. Entity must keep record of Individuals trained, dates, and means of verifying Individuals understood training.

- **Records - 73.15:** RO and Entity must keep up to date, accurate, verifiable records for 3 years of: (i)all Individuals approved by AG under 73.8; (ii) **Inventory** of agents/toxins with names, characteristics, sources, acquisition dates, quantities acquired; quantity of toxins on date of 1<sup>st</sup> inventory and held currently; quantity, volume, mass and date agent/toxin is destroyed/disposed of (see 5-day advance notice to HHS -73.7); quantity and dates of toxin's use; date, parties and quantities of agents/toxins transferred (including within Entity, even if all parties covered by same registration); agents/toxins lost, stolen, unaccounted for; written explanation of discrepancies; (iii) **Re: Access to Toxins/Agents,** name of each Individual who accessed agent/toxin, id of agent/toxin, dates agents/toxins removed and returned if from/to long-term storage or stock culture holdings, and, if toxin, quantity removed and returned; (iv) **Re: Access to Areas Where Agents/Toxins Used or Stored,** name of, date and time when, each Individual enters and leaves area where agent/toxin used or stored, and for Individuals not approved by AG under 73.8, the approved Individual who accompanied them; (v) **Safety inspections** (73.10(b)); (vi) **Safety, Security, Emergency Response Plans and Incident Reports;** (viii) **Training Records** (7.13); and (ix) **Transfer Documents and Permits** (73.14).
- **Notices - 73.17:** Entity must **immediately** notify (by fax, phone, e-mail): (i)Secretary HHS and state/local law enforcement, upon discovery of theft/loss of agent/toxin (name, characteristics, estimated quantity, estimated time, location), even if recovered and responsible parties identified; and (ii)Secretary HHS and state and local public health agencies, of any release causing occupational exposure or outside primary containment barriers (name, characteristics, hazards posed, estimated quantity, time and duration, environment into and location from which release occurred, number of people potentially exposed at facility, response actions taken); and (iii) within 7 days of theft/loss/release, Entity must submit written report to HHS Secretary (7.21).
- **Inspections by HHS Secretary -73.16:** Without notice, without cause, Secretary may inspect site where regulated activities occur, and inspect and copy records relating to such activities.
- **Administrative Review, Civil and Criminal Penalties - 73.18-73.20:** Administrative Review of adverse 73.7 or 73.8 decision must be requested (73.21) within 30 days of decision. Criminal and civil penalties apply to Individuals and Entities that violate 42 CFR Part 73.
- **Forms and Notice/Submission Protocols -73.21**
- [\*Post 2/7/03 Agents/Toxins: **AG Security Approval and Registration Application:** Entity and Individuals may not use, possess, receive or transfer any new agent/toxin – those not acquired and covered by a registration, or grown, created, otherwise lawfully possessed, as of 2/7/03 – from 2/7/03 -11/11/02, unless they obtain a US AG Security Approval by 2/7/03 and submit a request for registration to HHS Secretary by 2/6/03. (42 CFR 73 (c)(4)). On and after 11/12/03, all new requirements, including obtaining a new registration, apply before new agents/toxins can be acquired, grown or created.]

**Issue:** How do we make/keep required 73.15 access (to agents/toxins and to their use and storage areas) security records by 2/7/03, before the date we are required to implement our security plan? Physical infrastructure won't be in place. (Security plan: 6/12/03 development and 9/12/03 implementation deadlines.)

**Issue:** There is a small window, from now through 2/6/03, in which to receive a registration to cover any new agents/toxins not presently covered by a registration or lawfully possessed (already grown or created), that will be needed from 2/7/03-11/11/03. May PI grow/create toxin through 2/6/03?

**3/11/03 Effective Date (42 CFR 73.0(b)(1) and (2))**

\*[2/6/03 for new agents/toxins after 2/7/03]

- **Registration Application - 73.7:** Entity must have submitted application for registration to HHS Secretary by this date, or may not use, possess, receive, transfer select agents or toxins from 3/12/03-11/11/03 – includes certification of compliance with 73.13 (training on safety and emergency response), 73.1-73.6 (definitions, scope, general prohibition, lists and exemptions), 73.9 (RO), 73.10 (safety plan), 73.12 (emergency response plan), and 73.15-73.21 (records; inspections; notices of theft, loss, release; enforcement, penalties, and forms).  
\*[2/7/03 73.8 is in effect for new agents/toxins after 2/7/03]

<p>*[2/7/03 73.8 effective for new agents/ toxins after 2/7/03]</p>	<ul style="list-style-type: none"> <li>• <b>Security Risk Approval Request - 73.8:</b> Entity must have <u>requested security approval</u> of <u>Entity, RO, all Individuals Owning or Controlling Entity</u>, from US AG by this date, or <u>may not</u> use, possess, receive, transfer select agents or toxins from <u>3/12/03-4/11/03</u></li> </ul> <p><b>Issue:</b> What happens if we timely file registration and AG security risk approval requests, but HHS Secretary and/or AG don't respond by phase-in deadlines for registration or AG security risk approval? 73.3's general prohibition and 73.7 and 73.8 state we can't use, possess, receive, or transfer agents/toxins without registration and AG security risk approval.</p> <p><b>Issue:</b> Are the Trustees, Board Members, Corporation Members, Stockholders, Senior Officers, other Individuals of Entities who either control or have ownership interests in the Entity subject to AG background checking? Read literally, the regulations say "yes". Will all stockholders of large public corporations be covered? Nonprofit entities don't have "owners," but how far is "control" taken?</p>
<p><b>3/12/03 Effective Date (42 CFR 73.0(a)(3))</b></p>	
<p>*[2/7/03 for new agents/ toxins after 2/7/03]</p>	<p><b>Transfers - 73.14:</b> Entity <u>cannot transfer</u> agents/toxins to another Entity in the US, <u>or receive</u> agents/toxins from an Entity outside the US, <u>unless</u> US sender and US recipient satisfy CDC approval and documentation requirements of 73.14, have relevant registrations under 73.7; sender from outside US satisfies all import requirements; all senders comply with packaging and shipping laws; RO sends documentation to HHS Secretary within 2 days of receipt of agent/toxin; and recipient notifies HHS Secretary within 48 hours after expected delivery time if agent/toxin not received or if package is leaking or damaged. <u>Recipient must notify HHS Secretary of agents/toxins consumed or destroyed after a transfer, within 5 business days (73.21).</u> <u>Does not apply to intra-Entity transfers when sender and recipient are covered by the same registration certificate.</u></p> <p><b>Issue:</b> How do we track/report consumption of agent?</p>
<p><b>4/11/03 Effective Date (42 CFR 73.0(b)(3))</b></p>	
	<p><b>Security Risk Approval Request:</b> <u>Entity</u> must have requested <u>security risk approval</u> of all <u>Individuals requiring access to agents/toxins</u> (other than those subject to the 3/11/03 deadline) <u>from US AG under 73.8 by this date</u>, or <u>may not</u> use, possess, receive, transfer select agents or toxins from <u>4/12/03-6/11/03</u>.</p> <p><b>See issues under 3/11/03.</b></p>
<p><b>4/12/03 Effective Date (42 CFR 73.0(a)(4))</b></p>	
<p>*[2/7/03 for new agents/ toxins after 2/7/03]</p>	<p><b>Security Risk Approval - 73.8:</b> Must be obtained for <u>Entity, RO, Individuals Owning or Controlling Entity from the US AG by this date</u>. Entity <u>may not</u> possess, use, transfer within the US, or receive from outside the US, agents/toxins unless approved by the Secretary of HHS (or USDA, as applicable), based on a security risk approval from the AG. <u>Entity may not provide access</u> to Individuals to, and <u>Individuals may not access</u>, agents/toxins, unless Individuals are approved by Secretary of HHS (or USDA, as applicable) based on security risk approval from the AG. <u>Entity</u> must submit application for Entity, RO, all Individuals, to AG. Required information/application form, not yet available. <u>There is no time limit for AG's review. Entity to receive "prompt" notice of action taken; Individuals to receive "prompt" notice of denial of approval.</u> HHS Secretary may ask for <u>expedited review for "good cause" determined by the Secretary</u>, including impending expiration of grant or short-term visit of "prominent" researcher. <u>AG will notify HHS Secretary if Entity or Individual (i)is "restricted person" under the USA Patriot Act, in which event Secretary will deny or revoke approval; or (ii)is "reasonably suspected by federal law enforcement or intelligence agency" of committing certain violent or terrorist crimes, being knowingly involved with an organization that engages in domestic or international terrorism or intentional violent crimes, or is an agent of a foreign power, in any which event, the Secretary will deny or revoke approval,</u> if Secretary determines this is warranted for public health, safety or national security, <u>or may allow limited access if so warranted.</u> Security risk approval is <u>valid for 5 years</u>, unless a shorter period is specified, or unless terminated, by HHS Secretary.</p>

	<b>See issues noted under 3/11/03.</b>
<b>6/12/03</b>	<b>Effective Date (42 CFR 73.0(a)(4) and (5))</b>
*[2/7/03 for new agents/ toxins after 2/7/03]	<b>Security Risk Approval - 73.8:</b> Must be obtained for all Individuals who need access to agents/toxins (other than RO and others subject to 4/12/03 deadline) from the US AG by this date. See 4/12/03 Effective Date for description of substantive requirements and issues that apply to Individuals as well.
*[9/12/03 for new agents/ toxins after 2/7/03]	<p><b>Develop Security Plan - 73.11:</b> Entity must <u>separate areas where agents/toxins are stored or used from “public areas of buildings”</u> (i.e., areas not secured as follows) and <u>develop security plan</u> that identifies threats, examines and mitigates vulnerabilities, and employs a systematic approach to security, <u>covering areas</u> where agents/toxins are located and <u>must include:</u> (i) <u>Inventory controls</u> (73.15); (ii) <u>Minimal education/experience standards</u> for Individuals with access to agents/toxins; (iii) <u>Physical and Cyber Security</u>; (iv) <u>Routine Cleaning/Maintenance/Repair</u> procedures; (v) <u>Security Training</u> for all Individuals with access to agent/toxin areas or containers, including non-lab workers and visitors who are escorted; (vi) <u>Card, keypad, other Access Security with Unique Access Codes for each Individual, and protocols</u> to change access numbers upon staff changes, for loss/compromise of keys, passwords, etc.; to report and remove suspicious or unauthorized people; report loss/theft/release of agents/toxins; report alteration of Inventory; (v) <u>Security for Containers;</u> (vi) <u>Allowing Unescorted Access to Areas</u> only to AG-approved (73.8) Individuals during hours necessary to do a specified job and only for a specifically authorized function, <u>and</u> to Individuals who did not seek clearance under 73.8 but need access for cleaning or other <u>non-lab functions</u> <u>and</u> who are escorted and continually monitored by an approved Individual; (vii) <u>Locking agent/toxin containers</u>, and, if necessary, video surveil them, whenever not in direct view of an approved Individual; (viii) <u>Inspection of all Packages on Entry to and Exit from areas with toxins/agents;</u> (ix) <u>Intra-Entity agent/toxin transfer protocols</u>, with those AG-approved under 73.8 supervising packaging and moving agents/toxins; (x) <u>Prohibiting Individuals from sharing their unique area and container access codes;</u> <u>and</u> (xi) <u>Requiring Individuals approved under 73.8 to Immediately report to RO</u> loss/compromise of keys, passwords, etc., suspicious persons/activities, loss/theft/release of agents/toxins, any “sign” of inventory/records being compromised; <u>or</u> (xii) <u>Can propose equivalent alternatives to (vi)-(xi).</u> RO must review plan at least annually and after an incident. <u>Upon termination of use, agent/toxin must be securely stored, transferred under 73.14, or destroyed on-site using autoclaving, incineration, or other recognized sterilization/neutralization approach.</u> (See <u>5 business day advance notice to Secretary of HHS of destruction</u> for discontinuance under 73.7(h)(registration).)</p> <p><b>See issues under 2/7/03 Effective Date re: record-keeping requirements before security plan.</b></p> <p><b>Issue: Does checking “packages” upon entry to and exit from areas with agents/toxins include backpacks and pocketbooks, or just delivery packages?</b></p>
<b>9/12/03</b>	<b>Effective Date (42 CFR 73.0(a)(2) and (5))</b>
*[9/12/03 new agents/ toxins after 2/7/03]	<ul style="list-style-type: none"> <li>• <b>Implement Security Plan - 73.11:</b> See 6/12/03 Effective Date for substantive provisions.</li> </ul>
*[2/7/03 for new agents/ toxins after 2/7/03]	<ul style="list-style-type: none"> <li>• <b>Training In Security and Rest of Part 73 - 73.13:</b> See 2/7/03 Effective Date for Training on Safety and Emergency Response for provisions that apply to Security Training as well.</li> </ul>

2/7/03]	
<b>11/12/03 Effective Date (42 CFR 73.0(a)(6))</b>	
*[11/12/03 new agents/ toxins after 2/7/03]	<ul style="list-style-type: none"> <li>• <b>Registration - 73.7:</b> Entity may not possess, use, transfer within US or receive from outside US, agents/toxins unless it has a Certificate of Registration from the HHS (or USDA, as applicable) Secretary, and must apply by: (i) obtaining registration application no. from HHS; (ii) applying for Security Risk Approval from US AG under 73.8 for Entity, RO, Individuals who own or control Entity; (ii) submit for Entity, RO, Individuals, AG-assigned ID. no. under 73.8 and their names, addresses, contact nos.; names, sources, characterizations, quantities held (at application time) of agents/toxins; Safety, Security, Emergency Response Plans; Training; Building, room, floor plans where agents/toxins stored or used; List of all Individuals needing access; Certification of accuracy by RO; and any other necessary information; (iii) applies to activities at one location (can be complex of buildings at one mailing address); (iv) valid for <u>up to 3 years</u>, only for <u>agents/toxins, activities, locations in application</u>, and RO must promptly notify HHS Secretary (73.21) of any change in application information (areas of work, protocols, objectives of study, people approved under 73.8, etc.); (v) <u>apply for new registration at least 8 weeks before expiration</u> to "help ensure" timely review, but <u>no deadline for issuing registration</u>; (vi) HHS Secretary will terminate registration when registered activities cease, for any violation of Part 73, for security risk (based on AG review 73.8), or if necessary for public health or safety, and Entity must transfer or destroy agent/toxin per HHS directions upon termination of registration; (vii) Entity must notify HHS Secretary <u>at least 5 business days before destroying agent/toxin</u>, if discontinuing activities, and HHS may witness. Application including HHS agents/toxins and overlap agents/toxins must be submitted to HHS Secretary; one for overlap only may be submitted to HHS or USDA.</li> </ul>

**Please review full text of regulation for complete requirements (see [web.mit.edu/environment](http://web.mit.edu/environment)). This is a summary for general information only. Also, interpretations of provisions will likely change as HHS and Justice provide more guidance.**

Jamie Lewis Keith, Senior Counsel, MIT 12/18/02

Select Agents Review of Changes: December 13, 2002  
Biosafety Programs

<u>HHS Select Agents</u>		
List in July, 2002	Changes to List as of December 12, 2002	Comment
Crimean-Congo Haemorrhagic Fever Virus	Same	The toxins have all been assigned a threshold, upper limit quantity, that once exceeded triggers the need to register. We will need to have a policy and mechanism in place so that quantities can be tracked in order to ensure that lab groups don't go over the threshold levels, that we can account for toxin materials.
Ebola Virus	Same	
Lassa Fever Virus	Same	
Marburg Virus	Same	
Rickettsia Prowazekii	Same	
Rickettsia Rickettsii	Same	
South American Haemorrhagic Fever Virus	Same	
Tick-borne Encephalitis Complex Virus	Same	
Variola Major Virus (smallpox virus)	Added variola minor assoc. viruses (new)	
Viruses causing Hantavirus Pulmonary Syndrome	Deleted	
<b>Yellow Fever Virus</b>	Deleted	
<b>Yersinia Pestis</b>	Same	
Abrin*	100mg per PI (new)	
Conotoxin*	100 mg per PI (new)	
Diacetoxyscirpenol*	1000 mg per PI (new)	
<b>Ricin*</b>	100 mg per PI (new)	
<b>Saxitoxin*</b>	100 mg per PI (new)	
<b>Tetrodotoxin*</b>	100 mg per PI (new)	
	Cercopithecine herpesvirus (new)	These were added by HHS
	Coccidioides posadasii (new)	

USDA-HHS Overlap Agents

List in July, 2002	Changes to List as of December 12, 2002	Comment
<b>Bacillus anthracis</b>	Same	
<b>Brucella abortus</b>	Same	
Brucella melitensis	Same	
Brucella suis	Same	
Burkholderia (Pseudomonas) mallei	Same	
Burkholderia (Pseudomonas) pseudomallei	Same	
Clostridium botulinum	C. botulinum neurotoxin producing strains	
Coccidioides immitis	Same	
<b>Coxiella burnetti</b>	Same	
Eastern Equine Encephalitis Virus	Same	
Morbillivirus (Hendra & Nipah Viruses)	Same	
<b>Francisella tularensis</b>	Same	
Rift Valley Fever Virus	same	
	Monkeypox virus (new)	
<b>Venezuelan Equine Encephalitis Virus</b>	same	
<b>Botulinum neurotoxins</b>	0.5 mg per PI (new) specified A-G neurotoxins	
Clostridium perfringens epsilon toxin*	100 mg per PI (new)	

<b>Aflatoxins*</b>	Deleted	
<b>Shigatoxin*</b>	And Shiga-like ribosome inactivating proteins, 100mg per PI (new)	
Staphylococcal enterotoxins*	5 mg per PI (new)	
T-2 toxin*	1000 mg per PI (new)	

Based on results of investigator surveys MIT has none of the agents listed below.

<b>USDA High Consequence Livestock Pathogens and Toxins</b>		
<b>List as of July 2002</b>	<b>Changes in List in December 2002</b>	<b>Comments</b>
African Horse Sickness Virus	Same	
African Swine Fever Virus	Same	
Akabane Virus	Same	
Avian Influenza Virus (highly pathogenic)	Same	
Blue Tongue Virus (exotic)	Same	
Bovine Spongiform Encephalopathy Agent	Same	
Camel Pox Virus	Deleted	
Classical Swine Fever Virus	Same	
Cowdria Ruminantium (Heartwater)	Same	
Foot and Mouth Disease Virus	Same	
Goat Pox Virus	Same	
Japanese Encephalitis Virus	Same	
Lumpy Skin Disease Virus	Same	
Malignant Catarrhal Fever Virus (exotic)	Same	
Menangle Virus	Same	
Mycoplasma capricolum/M.F. 38/M. mycoides capri	Same	
Mycoplasma mycoides mycoides	Same	
Newcastle Disease Virus (exotic)	specified velogenic strains	
Peste des petit ruminants Virus	Same	
Rinderpest Virus	Same	
Sheep Pox Virus	Same	
Swine Vesicular Disease Virus	Same	
Vesicular Stomatitis Virus (exotic)	Same	

<b>USDA High Consequence Plant Pathogens</b>		
<b>List as of July 2002</b>	<b>Changes in List in December 2002</b>	<b>Comments</b>
<i>Liberobacter africanus</i>		
<i>Liberobacter asiaticus</i>		
<i>Peronosclerospora philippinensis</i>		
<i>Phakopsora pachyrhizi</i>		
Plum pox potyvirus		
<i>Ralsonia solanacearum</i> Race 3	Specified Race 3 biovar 2	
<i>Sclerophthora rayssiae</i> var. <i>oryzicola</i>		
<i>Synchytrium endobioticum</i>		
<i>Xanthomonas oryzae</i> pv. <i>Oryzicola</i>		

<i>Xylella fastidiosa</i> (citrus variegated chlorosis strain)		
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Genetic Elements, Recombinant Nucleic Acids, Recombinant Organisms from December 13, 2002 regulation:

- Select agent viral nucleic acids (synthetic or naturally derived, contiguous or fragmented, in host chromosomes or in expression vectors) that can encode infectious and/or replication competent forms of any of the select agent viruses.
- Nucleic acids (synthetic or naturally derived) that encode for the functional form(s) of any of the toxins listed in the regulation if the nucleic acids are in a vector or host chromosome; can be expressed in vivo or in vitro ; or are in a vector or host chromosome and can be expressed in vivo or in vitro.
- Viruses, bacteria, fungi, and toxins listed in the regulation that have been genetically modified.