CHANGES TO THE HHS SELECT TOXINS REGULATIONS (FINAL RULE) AND GUIDANCE

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OUTLINE

- Section 3(d)(7)
- New limits for non-regulated amounts of HHS select toxins
- Due diligence
- Provisions for HHS select toxins identified in original food or clinical sample
- HHS select toxins that are produced as a byproduct of culturing select agents
- Exemptions
SECTION 3(D)(7)
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Section 3(d):
HHS select agents or toxins that meet any of the following criteria are excluded from the requirements of this part:

(7) Except as required in section 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:
SECTION 3(D)(7)

- 1000 mg of Abrin
- 1 mg of Botulinum neurotoxins
- 100 mg of Conotoxins
- 10,000 mg of Diacetoxyscirpenol
- 1000 mg of Ricin
- 500 mg of Saxitoxin
- 100 mg of Staphylococcal enterotoxins (subtypes A–E)
- 10,000 mg of T–2 toxin
- 500 mg of Tetrodotoxin
Provided that,
“(i) The toxin is transferred only after the transferor uses due diligence and documents the identification of the recipient and the legitimate need (e.g., prophylactic, protective, bona fide research, or other peaceful purpose) claimed by the recipient to use such toxin.”
Section 3(d)(7)(i) (Cont’d):
Information to be documented includes, but is not limited to, the recipient identity information, including the recipient’s name, institution name, address, telephone number and email address; name of the toxin and the total amount transferred; and the legitimate need claimed by the recipient.
Section 3(d)(7)(i) (Cont’d): The HHS Secretary retains the authority to, without prior notification, inspect and copy or request the submission of the due diligence documentation to the CDC.
Section 3(d)(7)(ii):
Reports to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in this part.
NEW LIMITS FOR NON-REGULATED AMOUNTS OF HHS SELECT TOXINS
## CHANGES IN EXCLUDED AMOUNTS OF TOXINS

<table>
<thead>
<tr>
<th>HHS-Regulated Toxin</th>
<th>Old Limit (mg)</th>
<th>New Limit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrin</td>
<td>100</td>
<td>1,000</td>
</tr>
<tr>
<td>Botulinum neurotoxins</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Conotoxins*</td>
<td>100</td>
<td>100 (unchanged)</td>
</tr>
<tr>
<td>Diacetoxyscirpenol</td>
<td>1,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Ricin</td>
<td>100</td>
<td>1,000</td>
</tr>
<tr>
<td>Saxitoxin</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>Staphylococcal enterotoxins (subtypes A-E)</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>T-2 toxin</td>
<td>1,000</td>
<td>10,000</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>100</td>
<td>500</td>
</tr>
</tbody>
</table>
The aggregate toxin amounts do not apply to regulated nucleic acids as any amount of these nucleic acids would be regulated.

A principal investigator (PI) is defined by the select agent regulations (SAR) as an individual who is designated by the entity to direct a project or program and who is responsible to the entity for the scientific and technical direction of that project or program.
NON-REGULATED LIMITS

With respect to a PI, an entity is not required to register with FSAP as long as each PI possesses less than the regulated amount of select toxin and meets all of the other exclusion requirements.
NON-REGULATED LIMITS

For an entity that is not registered:

- If one PI transfers select toxin to another PI such that the receiving PI now possesses an amount of toxin above the regulated amount, then the receiving PI and entity are both in violation of the SAR.
A select toxin derivative is a select toxin that possesses modifications, such as the addition of a hydroxyl group, that make them different from the parent molecule in nomenclature but still retain toxicity similar to the parent.
TOXIN DERIVATIVES

An example of a derivative that is regulated is the select toxin derivative HT 2. HT-2 has similar toxic properties as T-2.
Examples of unregulated non-toxic select toxins

- Ricin immunotoxin
- T-2 glucoside
- Toxin subunits such as the light chain of Botulinum neurotoxin (BoNT) or the Ricin subunit A only.
- Toxoids
DUE DILIGENCE
Section 3(d)(7)(i):
The toxin is transferred only after the transferor uses due diligence and documents the identification of the recipient and the legitimate need (e.g., prophylactic, protective, bona fide research, or other peaceful purpose) claimed by the recipient to use such toxin.
Section 3(d)(7)(i) (Cont'd):

- Information to be documented includes, but is not limited to, the recipient identity information, including the recipient's name, institution name, address, telephone number and email address; name of the toxin and the total amount transferred; and the legitimate need claimed by the recipient.
DUE DILIGENCE

Section 16(l):

- A registered individual or entity transferring an amount of a HHS toxin otherwise excluded under the provisions of section 3(d) must:
  - (1) Transfer the amounts only after the transferor uses due diligence and documents that the recipient has a legitimate need (e.g., prophylactic, protective, bona fide research, or other peaceful purpose) to handle or use such toxins.

Information to be documented includes, but is not limited to:
- The recipient information,
- Toxin and amount transferred, and
- Declaration that the recipient has legitimate purpose to store and use such toxins.
Section 16 (l) (Cont’d):

▪ (2) Report to CDC if they detect a known or suspected violation of Federal law or become aware of suspicious activity related to a toxin listed in section 3(d) of this part.
“Due diligence” is a measure of prudence, activity, or assiduity exercised by a reasonable and prudent person under the particular circumstances.

It is not measured by any absolute standard, but depends on the relative facts of the specific case.
FSAP developed the due diligence provision to address the concern that someone might stockpile select toxins by receiving multiple orders below the excluded amount.
The due diligence provision requires a transferor to take reasonable actions to ensure that the recipient is eligible to receive the select toxin because the recipient has a legitimate need to handle or use such select toxins.
It is the transferor’s responsibility to document how it has conducted its due diligence.

Due diligence records must be kept in accordance with the provision outlined in Section 17.
The transferor can document how they have determined that an individual (principal investigator, treating physician or veterinarian, or commercial manufacturer or distributor) has a legitimate purpose to handle and use such select toxins in a few ways:

- The transferor can have the recipient complete documentation stating their intended use of the select toxin.
- The transferor can document their own knowledge of the recipient’s legitimate need for the select toxin.
DUE DILIGENCE FAQS

- Does due diligence documentation go with every single transfer?
  - The sender must conduct due diligence on transfer recipients of toxin below the regulated amount. The sender needs to keep this information but the due diligence documentation doesn't have to physically accompany the transfer.

- Is a company or PI that possesses regulated amounts of a toxin able to transfer less than regulated amounts to unregistered entities or PIs without getting prior approval?
  - Yes, as long as due diligence is used to determine that the recipient has a legitimate need to handle or use such toxins.
PROVISIONS FOR HHS SELECT TOXINS IDENTIFIED IN ORIGINAL FOOD OR CLINICAL SAMPLE
PROVISIONS FOR HHS SELECT TOXINS IDENTIFIED IN ORIGINAL FOOD OR CLINICAL SAMPLE

Section 3(d)(9) and 4(d)(9):

- An HHS or Overlap select toxin that meets the following criteria is excluded from the requirements of the select agent regulations: “identified in an original food sample or clinical sample.”
Original food samples and clinical samples are those specimens that are submitted to laboratories for diagnosis or verification purposes to identify or verify a biological toxin. For example, these samples could be:

- A container of potato salad or juice.
- Serum or stool from a patient.
Laboratories that test food and clinical samples for the presence of toxins generally do not know the level of toxin in a sample and do not extract and purify a toxin as part of their studies.
PROVISIONS FOR HHS SELECT TOXINS IDENTIFIED IN ORIGINAL FOOD OR CLINICAL SAMPLE

- Any portions taken from the original sample would be regulated if toxin is identified.
  - The remaining original sample that was not subjected to testing is excluded.

- This exclusion does not pertain to samples (food or otherwise) spiked with known select toxin.
HHS SELECT TOXINS THAT ARE PRODUCED AS A BYPRODUCT OF CULTURING SELECT AGENTS
Section 3(d)(10):

- For those laboratories that are not exempt under § 73.5(a) and § 73.6(a), 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.
The regulatory starting point for BoNT is intentional BoNT collection, extraction, amplification, or production.

The natural environment for BoNT is Botulinum neurotoxin producing species of *Clostridium* for which no additional procedures have been done to collect, extract, amplify, or produce BoNT.
PROVISIONS FOR HHS SELECT TOXINS AS A BYPRODUCT

- Botulinum neurotoxin producing species of *Clostridium* are regulated and the byproduct exclusion only pertains to the toxin.
  - An entity will have to meet the provisions for registering a Tier 1 select agent.
- If the material containing the toxin is retained past 30 days, the toxin in the material will be subject to the regulations.
If an entity grows *Clostridium botulinum* and the intent is to study the organism and the supernatant (where the toxin is excreted) is discarded as waste, this would not be considered intentional cultivation or collection of the toxin.

Please see section 12(a)(3) for the documentation of material discarded as waste.
EXEMPTIONS
EXEMPTIONS FOR HHS SELECT TOXINS

Section 5(a)(1):
Unless directed otherwise by the HHS Secretary, within seven calendar days after identification of the select agent or toxin (except for Botulinum neurotoxin and/or Staphylococcal enterotoxin (Subtypes A–E)), or within 30 calendar days after identification of Botulinum neurotoxin and/or Staphylococcal enterotoxin (Subtypes A–E), the select agent or toxin is transferred in accordance with section 16 or destroyed on-site by a recognized sterilization or inactivation process.
EXEMPTIONS FOR HHS SELECT TOXINS

- This provision includes only BoNT and Staphylococcal enterotoxin (Subtypes A-E) because the identification for these toxins includes both agent and toxin as part of diagnosis.

- The extension of the exemption period from 7 to 30 calendar days allows clinical and diagnostic laboratories sufficient time to complete their investigations without having to transfer or destroy the sample before the investigation is complete.

- The 30 day time frame only applies to the transfer, destruction, or movement to select agent inventory. It does not apply to Form 4 reporting.
REFERENCES

- Select agent regulations
- Select toxin guidance document
- Select toxin FAQs
- Due diligence FAQs