Reporting the Identification of a Select Agent or Toxin in a Clinical or Diagnostic Laboratory

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Federal law necessitates that entities who possess, use, or transfer select agents or toxins which are deemed a severe threat to public, animal or plant health or to animal or plant products, be registered either with the US Department of Agriculture (7 DFR 331 and 9 CFR 121) or the US Department of Health and Human Services (42 CFR Part 73). Clinical laboratories however, are exempt from the provisions in this law since the only activity conducted by the laboratory concern select agents or toxins that are contained in specimens or in isolates from the specimen presented for diagnosis, verification, or proficiency testing. The law does require that laboratories, after confirmation of a select agent or toxin, transfer the specimen and isolate to a facility eligible to receive them or destroys the material on-site by some means sufficient to cause inactivation of the agent. As a part of this process, the laboratory is required to prepare a record of the identification and transfer or destruction on a form called, "Guidance Document for Reporting the Identification of a Select Agent or Toxin in a Clinical or Diagnostic Laboratory" (Animal and Plant Health Inspection Service [APHIS]/CDC Form 4). Laboratories that handle serum from a patient who is ultimately confirmed as positive for a select agent or toxin and who may have handled other specimens from this patient that were culture negative for a viable select agent, do not need to file Form 4. However, the laboratory must still immediately report serological confirmation of a select agent-caused disease to the county or State Department of Health. Be advised that multiple scenarios are present in the handling of specimens containing viable select agents and toxins and that ALL laboratories handling a specimen ultimately determined to contain a viable agent or toxin must file the CDC form. Described below (and in Tables 1 and 2 following the article) is the information needed to adequately file the APHIS/CDC Form 4. (The UNMC/NPHL Special Pathogens Laboratory, a unit within the Nebraska Public Health Laboratory [NPHL], is generally listed as the reference laboratory on Form 4 as the laboratory used for confirmation testing to identify a select agent or regulated toxin.)

Section 1 (all laboratories complete)

Legal name of entity. The legal entity refers to the reporting laboratory's official name.
Entity registration number. This number is recorded by the NPHL, while all other laboratories record "Not applicable".
Address. Self explanatory.
Name of facility director or responsible official, title, telephone, fax, and e-mail. Generally, this is the Laboratory Director but it may also be another responsible person such as the Biosafety Officer. This is the individual who also signs and dates the form after Section 5.
Select agent or toxin being reported. Include a scientific name.
Name of facility supervisor. Usually this is the supervisor of the laboratory handling the specimen.
Name/strain designation of the select agent/toxin. Record as "Not applicable"
Facility ID number. The specimen accession number is appropriate or leave blank.
Data regarding characterization. For laboratories submitting a specimen to a reference laboratory without doing any testing, indicate the following: "Specimen submitted to [list the laboratory] for isolation and/or confirmation". For laboratories submitting an isolate to a reference laboratory for confirmation testing, indicate the following: "Isolate presumptively identified as [give presumptive ID] using the following characteristics [list the methods used] was submitted to [list the laboratory] for confirmation testing". For laboratories performing confirmation testing indicate the following: "Confirmation identification performed using the following criteria: [list the criteria used]".
Location where work with specimens was conducted. For laboratories sending the specimen to a reference laboratory without testing, record "Not applicable". For all other laboratories performing some testing, identify the location of the laboratory.
Biosafety level. For laboratories sending a specimen to a reference laboratory without testing, record "Not applicable". For laboratories performing tests on the specimen and/or the isolate, list either BSL-2 or BSL-3 depending on the containment of the laboratory identified in the previous inquiry.

Section 2 (all laboratories complete)

Source of select agent isolate. For all laboratories handling the original specimen, check "Clinical or diagnostic specimen" and complete the species [presumably human] and the type of specimen [Other, may include multiple specimen types]. Check "Environmental sample" if from the environment. Check "Isolate" if the laboratory received an isolate for confirmation testing and indicate the name, address, and

telephone number of the laboratory that sent the isolate and the source. Indicate "Other" for situations that do not meet criteria for the other categories.

Name and telephone number of the person familiar with the case. Normally this is the primary physician of the patient from whom the specimen was obtained.

Description of the disease. Recorded by the laboratory who originally handled the specimen in consultation with the patient's primary physician. All other laboratories list "Unknown".

Number of isolates. For laboratories handling multiple specimens containing the select agent or toxin, record the actual number. For a reference laboratory doing confirmation testing, this usually will be 1 isolate.

Date of onset. Unless known otherwise, this is the date of specimen collection.

How diagnosis was made. Indicate either by "Serological" and/or by "Positive culture".

Laboratory that identified the agent. By and large this would be the "UNML/NPHL Special Pathogens Lab" or the lab may be some other reference facility.

Name, address, and phone of laboratory director. If the reference laboratory was the NPHL, use the following information: Steven Hinrichs, MD, 986495 Nebraska Medical Center, Omaha, NE 68198-6495, 402-559-8301.

Sections 3 and 4 (Leave blank)

Section 3 of the form allows for bi-weekly reporting by veterinary diagnostic entities that identify select agents or toxins in areas where the agent is endemic or during outbreaks. Section 4 is used for the reporting of select agent or toxin contained in a specimen presented for proficiency testing. Contact personnel at the NPHL for advice on filing this information when needed.

Section 5 (all laboratories complete)

Date select agent or toxin was identified. Indicate the isolate confirmation date (whoever did confirmation testing can supply this date).

Amount of agent transferred, destroyed, or retained. The laboratory receiving a specimen and subsequently forwarding the specimen on to a reference laboratory for testing should indicate, "Specimen transferred to (indicate reference laboratory)" A laboratory receiving a specimen for culture and subsequently sending isolate or other material for confirmation testing to the NPHL should indicate, "Isolate transferred to the NPHL and left over specimen (list amount) and other culture material (list amount) destroyed" or "All specimen (list amount) and culture material (list amount) transferred to the NPHL". A laboratory receiving the specimen for culture and subsequently sending an isolate for confirmation testing to a reference laboratory other than the NPHL or doing in-house confirmation testing should indicate, "Specimen [list amount] destroyed and isolate [list amount] transferred (list reference laboratory)" [under this circumstance, additional paperwork will be necessary before a transfer of the isolate from a reference laboratory other than the NPHL where the identification was confirmed or from a local laboratory that does in-house confirmation testing can take place]. A laboratory retaining an isolate should indicate, "Isolate retained (list amount)". A certificate of registration with the Select Agent Program is necessary in order to retain a select agent (the NPHL has a certificate of registration to possess select agents and toxin.)

Disposition of select agent after identification. The laboratory that submits a specimen to a reference laboratory for testing should indicate "Other, Specimen submitted to reference laboratory for culture and confirmation testing". The laboratory that receives a specimen for culture and subsequently sends an isolate for confirmation testing to the NPHL should check, "Destroyed on site" and indicate date destroyed and the method of destruction. The laboratory that receives the specimen for culture and subsequently sends all specimen and culture material to a reference laboratory for confirmation testing should indicate , "Other, all materials submitted to reference laboratory for confirmation testing". The laboratory that receives the specimen for culture and subsequently sends an isolate for confirmation testing to a laboratory other than the NPHL (it is assumed that the laboratory has retained a subculture of the isolate submitted) or has done in-house confirmation testing should check "Transferred" and then call the NPHL personnel to make arrangements for transfer of the identified isolate [an APHIS/CDC Form 2 will need to be processed in consultation with personnel at NPHL]. **NOTE: NO TRANSFER IS TO OCCUR UNTIL FORM 2 HAS BEEN PROCESSED AND AN AUTHORIZATION NUMBER HAS BEEN ISSUED BY THE CDC.** A laboratory that receives an isolate for confirmation testing that is subsequently retained after confirmation [only registered laboratories such as the NPHL can retain these isolates] should check, "Retained".

Is the source expected to provide additional specimens? Usually, check "No" and the anticipated

quantity of specimens to be received is then "None" and the anticipated time period to receive specimen is "Not applicable"

Signature. The Laboratory Director [as indicated in Section 1 of the form] must sign and date the form prior to submission to the CDC.

Conclusion. As indicated in this review, there are many situations available whereby the APHIS/CDC Form 4 should be processed and submitted to the CDC. The CDC Select Agent Program has indicated [personal communication] that it is not unusual to have multiple copies of the form submitted from a variety of laboratories in reference to one specimen. Complete records are important and CDC personnel actually encourage laboratories to do multiple reporting. Sending samples to the NPHL for confirmation testing actually simplifies the necessary paperwork if a select agent is identified. Although an attempt was made to recognize the common scenarios that laboratories may encounter in the handling of these restricted agents, there will most likely be situations that arise whereby additional information will be needed to fill out and submit Form 4. When these questions occur, please do not hesitate to contact Dr. Iwen at 402-559-7774 for consultation.

Table 1. Who must complete and submit the APHIS/CDC Form 4?a,b

Laboratories who:

♦ Handle the original specimen that contained a viable select agent or toxin prior to submission to a reference laboratory for testing

♦ Conduct the initial plating of the specimen but submit the suspect isolate to reference laboratory for confirmation testing

♦ Conduct the initial plating of the specimen and perform confirmation testing.c,d

♦ Confirm the identification following isolate submissionc,d,e

(Select agent confirmation is performed at the NPHL in most circumstances)

a In many instances, multiple laboratories will handled a specimen containing a select agent or toxin, thus requiring multiple submissions of Form 4.

b Laboratories handling serum from a patient who ultimately is confirmed as positive for a select agent by serological testing only do not need to file Form 4, but are still responsible for reporting immediately the result to their county or to the Nebraska Health and Human Services. Go to http://www.hhs.state.ne.us/cod/codreport.htm for more information about disease reporting.

c The laboratory performing confirmation testing is responsible for contacting the CDC for those agents requiring immediate reporting (telephone 404-498-225, facsimile 404-498-2265, or e-mail [Irsat@cdc.gov]).

d Agents requiring immediate reporting are listed in the instructions for Form 4.

e The UNMC/NPHL Special Pathogens Laboratory has the reagents and protocols necessary to confirm the identification of a select agent or toxin.

Table 2. Checklist for the reporting of a select agent or toxin following diagnosis and verification.

♦ Report immediately to the CDC by telephone, facsimile, or e-mail when required a
Note: Only required for laboratories performing confirmation testing.
♦ Report immediately to the county or to Nebraska Health and Human Services. Go to http://www.hhs.state.ne.us/cod/codreport.htm for more information about disease reporting.
♦ Dispose of the select agent or toxin b,c Note: Either by transfer to the NPHL or by onsite destruction.
♦ Obtain a copy of the APHIS/CDC Form 4 from the CDC or NPHL web sited
♦ Complete sections 1, 2, and 5
♦ Make 3 copies of the completed form
♦ Send the original Form 4 to the CDC, one copy to the NPHL, and one copy retained by the laboratory for three years e

a The instructions to the APHIS/CDC Form 4 lists those agents requiring immediate reporting to the CDC (telephone, 404-498-2255; facsimile, 404-498-2265; or e-mail, Irsat@cdc.gov)

b Only laboratories registered by the Select Agent Program may retain materials containing a select agent or toxin.

c Subcultures of select agents identified by a reference laboratory other than the NPHL should be sent to the NPHL for banking.
Transfer of isolates with a confirmed select agent or toxin will require additional paperwork. Personnel at the NPHL will coordinate this transfer.

d Refer to the CDC website at http://www.cdc.gov/od/sap/downloads2.htm or to the NPHL website at http://www.nphl.org/news.html#Select to obtain Form 4.

e Send the completed form to the Centers for Disease Control and Prevention, Select Agent Program, 1600 Clifton Road NE, Mailstop E-79, Atlanta, GA 30333.