

**Expanded Access Investigational New Drug (IND) Application Protocol:**

**Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases**

**IND Sponsor: Centers for Disease Control and Prevention (CDC)**

**Protocol CDC IRB # 4167**

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This IND protocol for DAT from the CDC contains information intended to guide treating physicians regarding the use of investigational DAT. This document, and the contents within the document, should not be altered during reproduction without prior authorization from the CDC.

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## 1.0 OBJECTIVE

The purpose of this Investigational New Drug (IND) protocol is to provide access to diphtheria antitoxin (DAT) for emergency treatment of suspected diphtheria cases and, under exceptional circumstances, to provide passive, transient protection against diphtheria toxin in an exposed contact. A FDA-licensed diphtheria antitoxin product is unavailable in the United States.

## 2.0 BACKGROUND

Diphtheria is a clinical syndrome caused by an exotoxin produced by the bacterium *Corynebacterium diphtheriae*; non-toxin-producing strains of *C. diphtheriae* are not associated with the syndrome but can cause localized inflammation. Diphtheria is transmitted from person to person by respiratory droplets or contact with discharges from skin lesions. The severe local and systemic manifestations of diphtheria result after diphtheria toxin binds to a wide range of cells, including epithelial, nerve and muscle cells. The toxin interferes with enzymes necessary for protein synthesis, leading to cell damage and death. Local effects include severe inflammation and pseudomembrane (a firmly-adherent leather-like exudate that looks like a membrane) formation in the nose, and/or pharynx and/or larynx, which can progress to life-threatening airway obstruction. Systemic effects may occur from absorption of diphtheria toxin and include myocarditis, polyneuritis, and, rarely, renal failure.

There are four biotypes of *C. diphtheriae*: *gravis*, *mitis*, *belfanti* and *intermedius*. All four biotypes are capable of producing an identical exotoxin. No difference in pathogenicity has been demonstrated among the four biotypes. Some strains of *Corynebacterium ulcerans* can also produce an identical diphtheria toxin. A diphtheria-like illness can result for an infection caused by toxin-producing strains of *Corynebacterium ulcerans*.<sup>1</sup> The onset of disease is insidious. Following an incubation period of 1-5 days, low-grade fever begins and a pharyngeal pseudomembrane develops over 2-3 days, along with lymphadenopathy and diffuse systemic toxicity, resulting in a rapid, thready pulse, weakness, and irritability. Although the systemic effects of diphtheria can occur in the first week of illness, they usually occur later (1-2 weeks after onset for myocarditis, 2-8 weeks for neuritis).

The hallmark of suspected diphtheria is a low-grade febrile, membranous pharyngitis of insidious onset. In a minority of instances, diphtheria can result from an isolated diphtherial infection in the larynx, nasal lining, or skin. Other diseases that can occasionally produce a similar membranous pharyngitis include streptococcal pharyngitis and infectious mononucleosis. Patients who have been treated with immunosuppressive drugs can present with a membrane that mimics diphtheria. Isolated diphtherial laryngitis can usually be differentiated from *Haemophilus influenzae* type b epiglottitis, spasmodic croup, or the presence of a foreign body by the gradual onset of diphtherial disease. Differentiation of isolated diphtherial laryngitis from viral laryngotracheitis or bacterial tracheitis can be difficult on the basis of symptoms alone.

DAT was first produced in the 1890s and is still being produced using serum from horses that are hyperimmunized with diphtheria toxoid. The evidence for efficacy of DAT for the treatment of diphtheria is based on observations and studies done several decades ago. Mortality rates for clinical diphtheria frequently exceeded 50% in the pre-antitoxin era. Almost as soon as antitoxin was available, clinical experience showed dramatic declines in mortality in groups of patients treated with antitoxin compared to historical control groups or groups treated at hospitals not using antitoxin. In one controlled trial in which patients at a hospital were allocated to antitoxin treatment or no antitoxin treatment on an alternating day schedule, mortality in treated patients was 3.3% compared to 12.2% in untreated patients.<sup>2</sup> It was also shown that early treatment is critical, with the degree of protection from DAT inversely related to the duration of clinical illness preceding its administration. Mortality increased progressively within the interval from onset of illness to treatment, with a sharp increase from 4% mortality in those treated with antitoxin within 24-48 hours to 16.1% in those treated on the third day of illness.<sup>3</sup> Mortality rates

continued to increase with more prolonged intervals, reaching 29.9% in those treated 7 or more days after onset. Current thinking is that toxin fixes to susceptible cells early in disease and fixed toxin is not neutralized by antitoxin.<sup>4</sup>

The management of a patient with suspected diphtheria includes:

- 1) Administration of DAT as soon as possible after testing for hypersensitivity to horse serum; early administration of DAT is critical for survival.<sup>5</sup>
- 2) Establishing the diagnosis through appropriate bacterial cultures;
- 3) Administration of antibiotics; and
- 4) Appropriate supportive care including special attention to maintaining an adequate airway in the presence of laryngeal or extensive pharyngeal membranes and to careful monitoring for cardiac rhythm disturbances or other manifestations of myocarditis.

Diphtheria is currently a rare disease in the United States. The last cultured-confirmed cases of diphtheria with toxigenic *C. diphtheriae* was reported in 1999 and 3 cases of diphtheria-like illnesses caused by toxigenic *C. ulcerans* and 5 probable cases of diphtheria were reported from January 2000 through December 2015. A case of exudative pharyngitis with a positive culture for nontoxigenic *C. diphtheriae* was reported in 2014. In 2003, a fatal probable case of respiratory diphtheria was imported from Haiti, a country that is endemic for the disease.<sup>6</sup> Access to DAT is essential to ensure urgent and effective treatment of all cases of suspected diphtheria. There is evidence that toxigenic strains of diphtheria continue to circulate in at least limited areas of the United States.<sup>7</sup>

### 3.0 PRODUCT INFORMATION

With the discontinued manufacturing of a U.S. licensed DAT product by Connaught in 1997, access to DAT product in the U.S. has been through CDC under an IND program. A DAT product manufactured by the Instituto Butantan in São Paulo, Brazil is provided for use in the United States under this IND program. This product is similar to the previously licensed DAT.

DAT manufactured by Instituto Butantan is a sterile, transparent (clear) serum solution supplied in 10 mL ampoules containing 10,000 IU each. The composition of DAT is summarized in **Table 1**. DAT must be stored in the refrigerator at 2 - 8°C (36 – 46°F). DO NOT FREEZE. Once an ampoule is opened, the DAT serum solution should be used immediately.

**Table 1. DAT Composition – Each 10 mL Ampoule**

<b>Ingredient</b>	<b>Content</b>
Diphtheria Antitoxin (DAT) immunoglobulin antigen-binding fragments	10,000 IU
Phenol	35 mg (maximum)
0.85% physiological solution	10 mL

### 4.0 PROGRAM DESCRIPTION

This is a program to allow DAT treatment for patients with suspected diphtheria infection. Physicians requesting diphtheria antitoxin should contact the CDC’s Emergency Operations Center (EOC) at 770-488-7100. The CDC diphtheria duty officer will release DAT if, following the discussion, it is the decision of the treating physician to request and administer DAT. The treating physician may decide against using DAT after it is released. In requesting and obtaining DAT, the treating physician is agreeing to serve as a site investigator under the IND and acknowledging to comply with FDA IND regulations (please refer to Section 7.0 of this protocol).

## 5.0 ELIGIBILITY

### 5.1 Therapeutic Use

Patients who have probable or confirmed respiratory diphtheria are eligible to receive DAT. The Council of State and Territorial Epidemiologists approved of the following clinical case definition for respiratory diphtheria: an upper respiratory tract illness characterized by sore throat, a low grade fever, and an adherent membrane of the tonsil(s), pharynx, larynx, and/or nose.

Laboratory criteria for diagnosis: Isolation of *Corynebacterium diphtheriae* from a clinical specimen or histopathologic diagnosis of diphtheria.

Case classification: For reporting purposes, cases are classified as probable or confirmed:

Probable: a clinically compatible case that is not laboratory confirmed and is not epidemiologically linked to a laboratory-confirmed case

Confirmed: a clinically compatible case that is either laboratory confirmed or epidemiologically linked to a laboratory-confirmed case

A patient's eligibility for treatment will be determined through discussion between the CDC diphtheria duty officer and the treating physician.

DAT should be released and administered without delay to:

- A. All cases of respiratory diphtheria with laboratory-confirmed toxigenic *Corynebacterium diphtheriae* or diphtheria-like cases with laboratory-confirmed toxigenic *Corynebacterium ulcerans*.
- B. Probable cases. Diphtheria should be strongly suspected in a probable case-patient who is toxic in appearance and one or more of the following:
  - is without another clearly established diagnosis
  - has rapidly worsening illness
  - has history of recent travel to a country where diphtheria is endemic or epidemic
  - was exposed to travelers from countries with endemic or epidemic diphtheria
  - has history of recent contact with dairy animals,
  - was never vaccinated or is not up-to-date with diphtheria toxoid vaccination

For probable cases which are considered to have a low probability for diphtheria, the duty officer will encourage the treating physician to consider other diagnoses. However the final decision to request and administer DAT to a patient lies with the treating physician.

- C. Case-patients who have isolated or localized lesions in the nose, eye, skin, or other anatomical sites from which *C. diphtheriae* is obtained, and in whom there are signs of systemic toxicity (fever, tachycardia (myocarditis), and weakness (neuropathy)). Otherwise, DAT treatment is not routinely indicated for treatment of cutaneous diphtheria skin infection; toxigenic sequelae are rare when the infection is limited to the skin and when the case-patient is up-to-date on vaccination with diphtheria toxoid.<sup>8</sup>

## 5.2 Prophylactic Use

DAT is used prophylactically only under exceptional circumstances. Eligibility for prophylactic use of DAT will be limited to the following situations:

1. An individual who:
  - Has had known exposure to toxigenic *C. diphtheriae* (or possibly other toxigenic *Corynebacteria*) AND
  - Is not up-to-date for vaccination against diphtheria AND
  - Cannot be kept under surveillance for the development of clinical symptoms or is not available for follow-up of results of culturing for the diphtheria organism.
2. An individual who has suspected or known injection of diphtheria toxin (e.g., laboratorians).  
Needle sticks do not qualify as injections.

Each request for use of DAT for prophylactic use will require detailed discussion of all possible options with the diphtheria duty officer. Under the rare circumstances when these conditions are met, the recommended prophylactic dose of DAT is 10,000 units (after appropriate sensitivity testing). Patients in situation #1 above also should be given prophylactic antibiotics and appropriate up-date vaccination with diphtheria toxoid. Patients in situation #2 do not need prophylactic antibiotics because they have not been exposed to the bacteria.

## 6.0 DAT TREATMENT PROCEDURES

### 6.1 Informed Consent/Parental Permission

Written informed consent in compliance with 21 CFR 50 should be obtained before any program-related procedures are initiated. Consent via the enclosed Informed Consent/Parental Permission Form (**Appendix 1**) must be obtained from the patient before DAT is administered, if the patient is able to give consent. If the patient is unable to give consent, consent must be obtained from the next-of-kin or legal guardian/representative. The treating physician or designee will provide information on DAT in lay terms to the patient. Information about the nature of the program, the means by which the program is to be conducted, and the risks to the patient will be provided.

A single Informed Consent/Parental Permission Form will be used to obtain consent from adults or parental permission for minors. Waiver of assent for older children (7–17 years of age) has been granted by the CDC Institutional Review Board (IRB) for all patients under this protocol for the DAT administration. Parental permission will be sought in accordance with 21 CFR 50.55(c) for all minors aged 17 years and younger (permission of only one parent is required). Please see **Appendix 1**. The ultimate responsibility for decision-making for use of this product in minors lies with the parent or guardian.

If a patient is unable to respond and make wishes known about DAT treatment, and no next-of-kin or legal guardian/representative is available, and the patient's illness is life-threatening, per 21 CFR 50.23 "Exception from General Requirements", informed consent may be deemed not feasible and the treating physician can make the determination to administer DAT. Per 21 CFR 50.23, the patient's treating physician, acting as the site investigator, and a physician who is not otherwise participating in this treatment protocol, must document the following on the consent form:

1. Patient is confronted by a life-threatening situation necessitating the use of DAT.
2. Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally-effective consent from the patient.
3. Time is not sufficient to obtain consent from the patient's legal representative.

4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the patient.

If time is not sufficient to obtain the independent physician determination required above in advance of administering DAT to the patient, and in the treating physician's opinion, immediate use of DAT is required to preserve the life of the patient, the determinations of the treating physician shall be made and, within 5 working days after the use DAT, be reviewed and evaluated in writing (via documentation of the above criteria) by a physician who is not participating in this treatment protocol.

This IND protocol has been reviewed and approved by the CDC IRB and a local institution/hospital may elect to defer to CDC's IRB approval (see Appendix 7 for the approval letter). However, if the institution/hospital IRB elects to review this IND protocol rather than rely on CDC IRB's review, the documentation of the above evaluation must be submitted to institution/hospital IRB within 5 working days of DAT administration. If the institution/hospital IRB defers to CDC IRB as a central IRB, a copy of the evaluation documentation should be sent to CDC within 72 hours of DAT administration for notification to the CDC IRB. For hospitals that are precluded by local law or institutional policy from relying on another IRB, or hospitals that otherwise decide to perform their own IRB review, administration of DAT should not be delayed while waiting for local, hospital IRB review; FDA regulations allow, given the emergency situation, that a hospital does not need to obtain IRB approval before administration if this is the hospital's first time using DAT (after administering DAT they need to report to their hospital IRB within 5 working days). Subsequent DAT use at the same facility requires IRB approval (21 CFR 56.104(c)).

## 6.2 Precautionary measures

DAT is an equine serum product and precautionary measures are recommended for all patients.

Patients with the following history may be at increased risk of developing serious anaphylactic reactions upon receipt of equine-origin serum administered subcutaneously (SC), intramuscularly (IM), or intravenously (IV):

- Asthma, allergic rhinitis, or urticaria
- Asthma, allergic rhinitis, or urticaria or other symptoms of distress when in proximity to horses
- Previous injection of serum of equine origin

All patients should have the following:

- An appropriate history taken for factors suggesting increased risk
- Sensitivity testing to DAT\* (see Section 6.3)
- Careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

Patients with a history suggesting increased risk should have the following:

- Initial sensitivity testing (scratch/prick skin test and ID test) with a reduced dose (1:1,000)\* (see Section 6.3.A and B)
- Very careful monitoring during sensitivity testing and DAT administration for evidence of hypotension and bronchoconstriction

\*Patients with positive or equivocal sensitivity testing to DAT should have *desensitization* performed (see Section 6.4).



Personnel who test for sensitivity to or administer DAT should be trained to treat anaphylactic reactions. The necessary medications, equipment, and staff competent to maintain the patency of the airway and to treat cardiovascular collapse must be immediately available.

### 6.3 Tests for Sensitivity to DAT

A test for sensitivity to DAT should be carried out each time DAT is administered. Sensitivity to DAT may be assessed by two methods:<sup>9,10</sup> the scratch, prick, or puncture skin test is followed by an intradermal (ID) test if the skin test is negative. This order is recommended as the skin test is thought to be safe while the ID test has been reported to cause fatal anaphylactic reactions.

#### A. Scratch, prick, or puncture skin test

After cleaning a skin site on the volar surface of the patient's forearm with alcohol and air drying, make a superficial scratch, prick, or puncture using a sterile needle or other sterile sharp instrument, breaking the skin but not drawing blood.

In persons with a *negative history* for animal allergy and no prior exposure to animal serum, apply one drop of a 1:100 dilution of the serum in normal saline to the site.

In patients with a *positive history* for animal allergy or prior exposure to animal serum suggesting increased risk, apply one drop of a 1:1,000 dilution of the serum in normal saline to the site. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) control tests should also be applied to similar scratch, prick, or puncture sites. A positive scratch test is a wheal with surrounding erythema at least 3 mm larger than the negative control test, read at 15-20 minutes. The histamine control must be positive for valid interpretation; a positive response consists of a wheal at the scratch site surrounded by an erythematous area. If the scratch test is negative, an ID test is performed. If the scratch test is positive, follow procedures for desensitization (Section 6.4).

#### B. ID test

In persons with a *negative history* for animal allergy and no prior exposure to animal serum, administer a reduced dose of 0.02 ml of 1:100 saline-diluted serum ID; this quantity should raise a small ID wheal.

In patients with a *positive history* for animal allergy or prior exposure to animal serum suggesting increased risk, administer a reduced dose of 0.02 ml of 1:1,000 saline-diluted serum ID; this quantity should raise a small ID wheal. If the test is negative, repeat it using a 1:100 dilution.

Positive (histamine) and negative (physiologic saline) ID control tests should be applied. Interpretation of the ID test is done as with the scratch test.

A positive skin test indicates the probability of sensitivity with some correlation between the severity of the reaction on skin testing and the likelihood and severity of reaction to the DAT. However, a negative skin test does not preclude the possibility of an adverse reaction and DAT should still be administered cautiously. In addition, antihistamines (and possibly other drugs such as tricyclic antidepressants) administered previously can interfere with the results of skin testing for periods of one day or longer depending on the antihistamine.

### 6.4 Desensitization

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Patients with positive sensitivity testing to DAT or with a history suggesting increased risk from DAT administration (even with a negative or equivocal sensitivity test) should undergo *desensitization*. Tables 2 & 3 (appended) serve as guides for desensitization. Table 2 gives an IV regimen and Table 3 gives IM, SC and ID regimens.<sup>7</sup> The IV route is considered safer because it offers better control.

The personnel performing desensitization need to have the expertise to treat anaphylaxis and the necessary equipment and medications available. Some physicians recommend concurrent treatment with an oral or IM antihistamine with or without IV administration of a corticosteroid such as hydrocortisone or methylprednisolone. The protection from anaphylaxis afforded by giving DAT according to the desensitization treatment schedule requires that no interruption occur in the sequence of administration of doses; if an interruption occurs the protection is lost.

## 6.5 DAT Administration

### Route

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

### Temperature

Antitoxin should be warmed to 32 – 34°C (90 – 95°F) before injection. Warming above the recommended temperature should be carefully avoided because the DAT proteins will denature.

### Dosage

- A. Perform sensitivity tests, and desensitization if necessary.
- B. Give the entire treatment dose of antitoxin IV (or IM) in a single administration (except for series of injections needed for desensitization).
- C. The recommended DAT treatment dosage ranges are:

**Table 1. Pediatric and Adult DAT Dose<sup>8</sup>**

Diphtheria clinical presentation	DAT dose (units)
Pharyngeal or laryngeal disease of 2 days duration	20,000 – 40,000
Nasopharyngeal disease	40,000 – 60,000
Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck	80,000 – 100,000
Skin lesions only (rare case where treatment is indicated)	20,000 – 40,000

- D. Give children the same dose as adults.
- E. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reactions.

Appropriate antimicrobial agents in full therapeutic dosages should be started immediately upon suspicion of respiratory diphtheria (and ideally after specimen collection). For cutaneous diphtheria, antitoxin is rarely required (see Section 5.1.C), attention should focus on wound hygiene and antimicrobial agent treatment. The antibiotic of choice for treatment of cutaneous diphtheria is erythromycin or penicillin.

Any person with clinical symptoms of diphtheria should receive DAT as soon as it can be made available, without waiting for bacteriologic confirmation of the diagnosis. Supportive treatment should be continued until all local and general symptoms are controlled.

#### Prophylactic regimen

Prophylactic treatment with DAT can be considered for contacts but is recommended only in exceptional circumstances. (Please reference Section 5.2). Such exceptional circumstances should be discussed in detail with the CDC diphtheria duty officer. If it is concluded that a close contact may benefit from receiving DAT, DAT can be administered in addition to antimicrobial prophylaxis and immunization with diphtheria toxoid. Before administering DAT:

- A. Perform appropriate sensitivity tests.
- B. If sensitivity testing is negative, give 10,000 units IM.
- C. If sensitivity testing is positive, proceed with desensitization schedule outlined in Section 6.4, and then administer 10,000 units of DAT IM.

### **6.6 Possible adverse reactions following administration of DAT**

#### Anaphylactic Reaction

Although onset and severity are highly variable, anaphylaxis usually begins in susceptible patients within minutes after exposure to DAT; in general the more rapid the onset, the more severe the reaction. The major manifestations are 1) cutaneous, including pruritus, flushing, urticaria, and angioedema; 2) respiratory, including hoarse voice and stridor, wheeze, dyspnea, and cyanosis; and 3) cardiovascular, including a rapid, weak pulse, hypotension, and arrhythmias. Anaphylaxis is a major medical emergency.

In the event of an anaphylactic reaction, treatment will depend on the nature and severity of the reaction. Parenterally-administered epinephrine is the primary drug for all types of reactions. Antihistamines should also be given. Additional medications, depending on the severity of the reaction may include corticosteroids, alpha-adrenergic blocking agents, aminophylline, and beta-2 agonists.<sup>7</sup>

#### Febrile Reaction

When fever occurs, it usually develops twenty minutes to one hour after exposure to DAT. It is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature. Most febrile reactions are mild and can be treated with antipyretics alone; severe reactions may require other measures (tepid water baths, etc.) to reduce the temperature.

#### Serum Sickness

The symptoms of serum sickness are fever, maculopapular skin rashes, or urticaria in milder forms (90% of instances) with arthritis, arthralgia, and lymphadenopathy also possible in more severe forms. Rarely, angioedema, glomerulonephritis, Guillain-Barré syndrome, peripheral neuritis, or myocarditis can occur. The onset of symptoms is usually 7 to 10 days (range 5 –24 days) after initial exposure to DAT. Onset can be as short as several hours to 3 days after administration of DAT in persons who have received a dose of animal serum in the past; these individuals are also more likely to develop serum sickness. Mild cases of serum sickness frequently resolve spontaneously over a few days to 2 weeks. Medications that may be helpful include antihistamines, non-steroidal anti-inflammatory drugs, and corticosteroids.<sup>7</sup>

Febrile reactions and serum sickness are not IgE-mediated and therefore are not predicted by skin testing. The frequency of anaphylaxis and serum sickness is partially dependent on the frequency of previous administration of animal serums in the population; this frequency is now low. Recent data on the frequency of adverse reactions to horse serum products is extremely limited due to their infrequent use. In

a review of 1,433 diphtheria cases treated with antitoxin between 1940 and 1950, the frequency of adverse reactions was as follows: anaphylaxis, 0.6% (without any fatalities); febrile reactions, 4.0%; and serum sickness, 8.8%.<sup>6</sup>

Given the potential risk of serious adverse reactions related to DAT administration, DAT should be administered under close monitoring in a setting with appropriate medical intervention if needed.

The clinical determination regarding DAT treatment should be based on risk-benefit assessment and the clinical status of the patient. Given the life-threatening nature of respiratory diphtheria and the toxin neutralizing effect of DAT, treatment with DAT may potentially reduce morbidity and enhance survival of patients with diphtheria.

## **7.0 REQUIRED PATIENT MONITORING AND REPORTING OF ADVERSE EVENTS**

### **7.1 Patient Monitoring**

Since DAT is an investigational product, treating physicians have certain responsibilities regarding the use of DAT and must comply with to meet the U.S. Food and Drug Administration (FDA) regulations. This includes performing patient evaluation and monitoring, and recording and reporting requested information to CDC, such as any occurrence of serious adverse events (SAEs) during and following DAT administration as described in **Section 7.2**.

The treating physician is responsible for completing and returning the following forms within 14 days of DAT administration:

- Adult Informed Consent/Parental Permission and Child Assent Forms (**Appendix 1**)
- Diphtheria Antitoxin Treatment and Adverse Effects Form (**Appendix 2**)
- CDC Diphtheria Worksheet (**Appendix 3**)
- Information for Close Contacts (**Appendix 4**)
- If the patient voluntarily elected for optional blood draws (see Section 9.0), then complete and return **Appendices 5A, 5B, or 5C**, as applicable.
- Form FDA 1572 (Statement of the Investigator) with a treating physician's CV (**Appendix 6**)

Once completed, forms and any supplemental information should be transmitted by fax (404-639-3717) to CDC Drug Service.

### **7.2 Definitions of Adverse Events (21 CFR 312.32)**

Adverse Event (AE): Any untoward medical occurrence with the use of DAT in humans, whether or not considered related to DAT. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of DAT, without any judgment about causality.

Adverse Reactions (AR): Any AE for which there is a reasonable possibility that DAT caused the AE. It is a subset of all AEs for which there is a reasonable possibility that DAT caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between DAT and the AE. "Suspected adverse reaction" implies a lesser degree of certainty about causality than "adverse reaction."

Serious Adverse Event (SAE): An AE or suspected adverse reaction is considered "serious" if, in the view of either the treating physician or CDC, it results in any of the following outcomes:

- death
- a life-threatening AE (An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the treating physician or CDC, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused a death.)

- inpatient hospitalization or prolongation of existing hospitalization (excluding the hospitalization due to diphtheria infection)
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect (if DAT is administered during pregnancy)

**Serious and Unexpected Suspected Adverse Reaction (SUSAR):** An adverse reaction that is both unexpected (not consistent with the observed or expected risk information applicable to DAT) and also meets the definition of “serious” described above.

### 7.3 Recording and Reporting Adverse Events

#### **Treating physician reporting requirements to CDC:**

The treating physician, serving as the site-investigator for DAT, must report all AEs by means of the Diphtheria Antitoxin Treatment and Adverse Effects Form (**Appendix 2**). These may include AEs that the patient reports spontaneously, those the physician observes, and those the physician elicits in response to open-ended questions. SAEs and SUSARs (see **Section 7.2** for definitions) must be reported to CDC within 24 hours of occurrence or as soon as possible by contacting the CDC diphtheria duty officer who was consulted at the time of DAT release. If this individual cannot be reached, the CDC Emergency Operations Center should be contacted at 770-488-7100 to reach the CDC diphtheria duty officer on call.

#### **CDC reporting requirements to FDA and CDC IRB:**

All SAEs and SUSARs reported to CDC will be reviewed by the CDC Principal Investigator and treating physician, acting as the site investigator, to assess and determine causality to DAT. In making the causality assessment, the CDC Principal Investigator and treating physician will discuss the information available for each reported SAE/SUSAR while considering the temporal relationship between DAT administration and the SAE/SUSAR, the evidence for other causes of the SAE/SUSAR, and the known safety information about DAT.

Association with DAT will be classified into four causality categories:

- **Related:** A clinical or medical event, including laboratory test abnormality, occurring in a plausible time relationship to DAT administration, and cannot be explained by underlying disease/condition or concurrent drugs
- **Possibly related:** A clinical or medical event, including laboratory test abnormality, with a reasonable time sequence to administration of DAT, but could also be explained by underlying disease/condition or concurrent drugs
- **Unlikely to be related:** A clinical or medical event, including laboratory test abnormality, with a temporal relationship to DAT administration that makes a causal relationship improbable, and underlying disease/condition or concurrent drugs provide plausible explanations
- **Not related:** A clinical or medical event, including laboratory test abnormality, after careful medical consideration, are clearly and incontrovertibly due to causes other than DAT

Of the SAEs determined to be SUSARs (Serious and Unexpected Suspected Adverse Reaction; see **Section 7.2** for definition), those that are fatal or life-threatening will be reported to FDA by CDC as soon as possible, but no later than 7 calendar days after CDC’s initial receipt of the information (21 CFR 312.32(c)(2)). Other SUSARs will be reported to FDA by CDC within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1). All three (3) of the following definitions contained in the FDA requirement for expedited reporting must be met to qualify for expedited reporting to FDA by CDC: 1) Serious, 2) Unexpected, and 3) Suspected Adverse Reaction. AEs that do not meet the requirements for SUSAR expedited reporting will be reported to FDA in the IND Annual Report.

CDC will also report all SUSARs to CDC IRB according to CDC IRB’s policy and procedures.

## 8.0 LABORATORY TESTING

Although the decision to administer DAT in a suspected case of diphtheria must frequently be made in the absence of confirmatory laboratory evidence, it is essential to obtain the specimens to confirm the diagnosis early in the course of illness, and if possible, before the administration of antibiotics. The recommended specimens include the following:

- A. Throat, membrane (swabs or fragments), and nasal swab specimens for diphtheria culture. These are plated on special media (tellurite-containing media). The testing laboratory must be notified to look for *C. diphtheriae* so that the appropriate, special medium is used, and laboratory personnel must have the necessary expertise to process cultures for *C. diphtheriae*. In patients who have not yet had specimens collected for culture, or who have had cultures processed that were negative for *C. diphtheriae*, the CDC diphtheria duty officer may recommend that existing or new specimens be sent directly to the CDC Diphtheria Laboratory for culture and polymerase chain reaction (PCR) testing. Testing by PCR has the capability of identifying the *tox* gene of *C. diphtheriae* from swabs or from membrane specimens when cultures are negative. Tissue and swabs for culture and PCR should be maintained in transport medium or in a sterile container kept moist with sterile, non-bacterial static saline until they reach the laboratory. Specimens for culture and PCR *should not be placed in formaldehyde*.

All *C. diphtheriae* strains isolated should be forwarded to the CDC Diphtheria Laboratory (telephone 404 639-1231) for confirmation and toxigenicity testing.

- B. A serum specimen can be obtained from the patient before antitoxin administration and tested for diphtheria antibodies (IgG). A low titer level (< 0.01 IU/ml) indicates susceptibility but does not confirm the diagnosis. A high titer (> 0.1 IU/ml) suggests that a diagnosis is less likely to be diphtheria.

## 9.0 OPTIONAL BLOOD DRAWS

Diphtheria antitoxin (DAT) is obtained from horse serum and there is a risk for an allergic reaction to horse proteins. A laboratory in the United States, called MassBiologics of the University of Massachusetts Medical School, is working to develop a human antitoxin to treat diphtheria as an alternative to equine diphtheria antitoxin. In order to establish comparability and determine the optimal dose of human monoclonal antibodies required to treat diphtheria, it would be most helpful to determine the amount of diphtheria antitoxin antibodies in the blood of persons treated with DAT during illness and convalescence; this information is currently not available.

Participation is voluntary and non-participation will not affect receiving treatment by the patient.

The optional blood draws are for measurement of anti-diphtheria antibody levels before and after administration of DAT, a blood sample (5 mL) would be collected at the following six time points (for a total of 30 mL):

- Prior to DAT infusion
- One-hour post DAT infusion
- 1 DAY post DAT infusion
- 3 DAYS post DAT infusion
- 7 DAYS post DAT infusion
- 28 DAYS post DAT infusion or at time of hospital discharge (whichever is earlier)

Information to accompany the serum samples includes patient initials, sex, age, weight, date and time of DAT administration and dose of DAT administered.

If patient agrees to participate, the following appendices should be referenced and informed consent is required:

- Appendix 5: Instructions for Processing Serum Samples for MassBiologics and Sample Control Form
- Appendix 5A: Informed Consent/Parental Permission Form for Additional Blood Draws with the use of DAT for Suspected Diphtheria cases
- Appendix 5B: Assent for Additional Blood Draws with the use of DAT for Suspected Diphtheria cases aged 12-17 years old
- Appendix 5C: Assent for Additional Blood Draws with the use of DAT for Suspected Diphtheria cases aged 7-11 years old

#### **10.0 LOCAL AND STATE HEALTH DEPARTMENT NOTIFICATION**

It is a requirement that cases of suspected diphtheria (e.g., cases for whom DAT is requested) and known contacts be reported to local and state health departments. A physician who requests and administers DAT should notify the local and state health departments. The CDC duty officer will also notify the state health department of any DAT that is released.

Public health officials will assist in identifying contacts at risk of infection, will often obtain nasal and throat swabs for cultures, and will facilitate antibiotic prophylaxis of contacts (oral erythromycin or penicillin) when necessary to prevent spread to other members of the community. All asymptomatic, unimmunized contacts of patients with diphtheria should receive prophylactic antimicrobial therapy after specimens for cultures are obtained. Nasal and throat swabs for culture should be obtained again after treatment. Immunization with diphtheria toxoid should be given, if not up-to-date, and surveillance for illness continued for seven days. This is the standard of care for contacts of a diphtheria case. Please see “Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures: recommendations of the Immunization Practices Advisory Committee (ACIP)” MMWR 1991:40 (No. RR-10)<sup>8</sup> for additional details.

#### **11.0 DATA COLLECTION AND STORAGE**

A requirement for release of DAT under this IND is that CDC will obtain and store information relating to the patient’s illness (including patient identifiers). Data obtained will be shared with the state health departments for public health investigation. In the event of serious adverse reactions, complete medical records may be requested for evaluation by the CDC Principal Investigator from the treating physician. SAEs and SUSARs will be reported to CDC IRB and FDA. Stored data will be analyzed as needed by CDC staff to prepare annual summary reports for renewal or continuation of the program with the CDC IRB and FDA. The data containing personal identifiers will be stored in locked file cabinets. This information will be kept strictly confidential. All forms should be returned directly to the CDC Drug Service.

CDC Drug Service, Mailstop D-09  
 1600 Clifton Rd. NE  
 Atlanta, GA 30329  
 Phone: 404-639-3670  
 Fax: 404-639-3717

**Table 2. Desensitization to DAT - Intravenous Route<sup>7</sup>**

<b>Dose Number*</b>	<b>Dilution of DAT in Normal Saline</b>	<b>Amount of Injection (cc)</b>
1	1:1,000**	0.1
2	1:1,000	0.3
3	1:1,000	0.6
4	1:100**	0.1
5	1:100	0.3
6	1:100	0.6
7	1:10**	0.1
8	1:10	0.3
9	1:10	0.6
10	undiluted	0.1
11	undiluted	0.2
12	undiluted	0.6
13	undiluted	1.0

\* Administer at 15 minute intervals.

\*\*1 ml (antitoxin) + 9.0 ml of saline = 1:10 dilution  
1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution  
0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution  
[1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution]



**Table 3. Desensitization to DAT - Intradermal, Subcutaneous and Intramuscular Route<sup>7</sup>**

<b>Dose Number*</b>	<b>Route of Administration</b>	<b>Dilution of DAT in Normal Saline</b>	<b>Amount of Injection (cc)</b>
1	ID	1:1,000**	0.1
2	ID	1:1,000	0.3
3	SC	1:1,000	0.6
4	SC	1:100**	0.1
5	SC	1:100	0.3
6	SC	1:100	0.6
7	SC	1:10**	0.1
8	SC	1:10	0.3
9	SC	1:10	0.6
10	SC	undiluted	0.1
11	SC	undiluted	0.2
12	IM	undiluted	0.6
13	IM	undiluted	1.0

\*Administer at 15-minute intervals.

\*\*1 ml (antitoxin) + 9.0 ml of saline = 1:10 dilution  
1 ml (1:10 dilution) + 9.0 ml of saline = 1:100 dilution  
0.2 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution  
[1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution]

## 12.0 REFERENCES

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