IND Protocol: Use of Pentavalent (ABCDE) Botulinum Toxoid Aluminum Phosphate Adsorbed (PBT) for Workers at Risk of Occupational Exposure to Botulinum Toxins

BB-IND 161

Protocol CDC IRB #392, Version 8.0

Sponsored by:

Centers for Disease Control and Prevention
Atlanta, GA

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APPENDICES

1.0 INTRODUCTION & BACKGROUND

Botulism is caused by neurotoxins produced by the bacterial pathogen *Clostridium botulinum* or other closely related bacterial species (e.g., *C. baratii* type F, *C. butyricum* type E, and *C. argentinense* [which is the defined species that produces type G]). The clinical manifestations of botulism result from the binding of botulinum toxin to nerve endings at neuromuscular junctions with resulting blockage of acetylcholine release. This leads to paralysis of voluntary muscles, including respiratory muscles, and can also lead to dry mouth, ileus, and urinary retention (see Table I); sensory nerves are unaffected. Invariably, cranial nerves are the first to be affected, with ptosis and inability to focus often the earliest findings. It may be recognized by its classic triad: 1) symmetric, descending flaccid paralysis with prominent bulbar palsies in 2) an afebrile patient with 3) clear sensorium.

Table I: Symptoms and physical findings in patients with types A and B foodborne botulism*

	Type A[b]	Type B[b]	Significant Difference ($p<0.05$)
Symptoms			
Neurologic Symptoms			
Dysphagia	96	97	0
Dry mouth	83	100	0
Diplopia	90	92	0
Dysarthria	100	69	+
Upper extremity weakness	86	64	0
Lower extremity weakness	76	64	0
Blurred vision	100	42	+
Dyspnea	91	34	+
Paraesthesia	20	12	0
Gastrointestinal symptoms			
Constipation	73	73	0
Nausea	73	57	0
Vomiting	70	50	0
Abdominal cramps	33	45	0
Diarrhea	35	8	+
Miscellaneous symptoms			
Fatigue	92	69	0
Sore throat	75	39	+
Dizziness	86	30	+
Physical Finding			
Cranial nerve examination			
Ptosis	96	55	+
Hypoactive gag	81	54	0
Ophthalmoplegia	87	46	+
Facial palsy	84	48	+
Tongue weakness	91	31	+
Pupils fixed or dilated	33	56	0
Nystagmus	44	4	+
Ataxia	24	13	0
Extremity power			
Upper	91	62	+
Lower	82	59	0

	Type A[b]	Type B[b]	Significant Difference ($p<0.05$)
Deep tendon reflexes			
Hypoactive or absent	54	29	0
Hyperactive	12	0	0
Altered sensorium	12	7	0

*Adapted from Hughes *et al*., 1981

[a] Data obtained from the hospital or physician office records of 55 patients with foodborne botulism reported to the Centers for Disease Control during the period 1973-1974.

[b] Percentage of patients developing symptoms or signs.

There are seven different types of botulinum neurotoxins: A, B, C, D, E, F, and G. Types A, B, C, D, E, and F have been documented to cause human disease. However, human cases of botulism types C and D are rare and they occur with more frequency in animals. Disease can occur following ingestion of preformed toxins present in contaminated food (foodborne botulism), from intestinal contamination by neurotoxin producing *Clostridia* species (infant botulism and intestinal colonization), contamination of a wound (wound botulism), or from breathing aerosolized toxin. In general, type A neurotoxin causes more severe disease in terms of bulbar and skeletal muscle impairment, need for ventilatory support, and length of hospitalization. In contrast, signs and symptoms of autonomic dysfunction (internal ophthalmoplegia with non-reactive dilated pupils and dry mouth) may be more frequent with types B and E neurotoxins (1-3).

The absence of sensory symptoms along with normal cerebrospinal fluid distinguishes botulism from Guillain-Barré syndrome (GBS), although CSF protein may be normal early in the course of GBS. Pupillary dysfunction may also occur in botulism, distinguishing it from myasthenia gravis. Electrodiagnostic testing can provide a definitive diagnosis if the characteristic augmented response to rapid repetitive stimulation (>20 Hz) is observed (1, 4).

Pentavalent (ABCDE) Botulinum Toxoid Aluminum Phosphate Adsorbed (PBT) is a combination of aluminum phosphate-absorbed toxoid derived from formalin-inactivated, partially purified types A-E botulinum toxins. For over 35 years, CDC has distributed PBT as an investigational vaccine under BB-IND 161 for protection of workers at risk of occupational exposure to botulinum toxins.

Experience with PBT has shown that: (a) it has been effective in protecting animals against intraperitoneal challenge with types A, B, C, D, and E toxins of *Clostridium botulinum*, (b) the serum antitoxin levels in animals as determined by mouse protection tests correlate with protective activity, and (c) the toxoid introduced into man has historically produced levels of antitoxin thought to be protective as judged by extrapolation of data derived from animal experiments.

In experiments with the original lot of toxoid (5, 6), 30 persons were immunized on a 0–2–12 week schedule. Antitoxin titers were detectable for all 5 types of toxin in about 80% of the volunteers 2 weeks after the initial series. These titers declined during the next 12 weeks and only a small percentage had measurable titers by one year, just before the boosters were given. Eight weeks after the boosters, 100% of the recipients had measurable titers to all 5 types.

In 1988 the U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) evaluated immunized subjects for neutralizing antibodies to types A & B botulinum toxins. After the primary series, 91% of subjects had a type A titer $\geq$ 0.08 IU/mL, and 78% of subjects had a type B titer $\geq$ 0.02 IU/mL. After the first booster, all individuals tested had a demonstrable titer for type A & B (7).

The Joint Vaccine Acquisition Program (JVAP) sponsored a clinical study with the PBT vaccine, Lots PBP003 and PBP004, under BB-IND 3723. This study entitled "Evaluation of Safety and Immunogenicity of Pentavalent Botulinum Toxoid (A-E) Administered to Healthy Volunteers" (also known as the "Harris Study"), was conducted from July 1998 to May 2000 and assessed the requirement for a 6-month dose of PBT. After receiving the primary series (0, 2, and 12 weeks) of PBT Lot PBP003, the percentage of vaccinees at 6 months with antitoxin antibody levels above the predetermined protective "benchmark" level were Type A: 30.8%; Type B: 58.3%; Type C: 60.9%; Type D: 32.3%; and Type E: 18.8% (8-10). Benchmark levels were 0.20, 0.014, 0.058, 0.055, and 0.014 IU/mL for serotypes A, B, C, D, and E, respectively. These are the serum concentrations at which 80% of guinea pigs, passively immunized with human botulinum antitoxin, survived 25 times a lethal aerosol challenge dose of botulinum toxin [25 LCt_{50}]) (11). Participants were actively monitored for occurrence of local and systemic side effects. An analysis of safety data from the initial study phase yielded findings consistent with historical experience with PBT; that is, no serious local or systemic reactions definitely attributable to the vaccine were observed. Results of the study with Lot PBP004 were similar to Lot PBP003, with the exception that antitoxin titers elicited to toxin serotype B were statistically higher with Lot PBP003 than Lot PBP004 (10). A 6-month dose of PBT resulted in increased antitoxin levels at 4 weeks post-vaccination, but these antitoxin levels declined again by month 12 to levels observed before the 6-month dose. These data suggested that a 6-month dose of PBT was necessary to maintain adequate antitoxin titers, and that the 12-month booster dose was still required to maintain protective titers (8-10, 12-13). These are also the levels, based on models of battlefield exposure, to afford protection against aerosolized *C. botulinum* rather than possible exposure in a laboratory setting (8).

2.0 OBJECTIVES

The purpose of this study is to ensure availability of the PBT vaccine to workers at risk of occupational exposure to botulinum toxins. The objective is to induce an immune response to botulinum toxins A-E that may offer increased protection from botulinum toxin exposure in a laboratory setting.

3.0 RISK/BENEFIT ASSESSMENT

Risks to Volunteer Subjects

Based on over 35 years of experience with vaccine administration by CDC under BB-IND 161, PBT appears to have an acceptable safety profile. Results of analysis of reactions from PBT vaccination from 1970 to 2008 (N=25,220) are described in Section 6.0.

Lot PBP004, to be used in this study, passed potency testing in 1999. However, potency testing in March 2001 and May 2002 showed failed potency resistance to challenge of PBT Lot PBP004 to toxins B, D, and E and Lot PBP003 to toxins D and E. Potency testing in May 2002 showed inconclusive or failure of potency antibody induction to specific antigens. Lot PBP004 failed antibody induction to toxin D and produced inconclusive results for the other toxins. Lot PBP003 failed antibody induction to toxins B and D and produced inconclusive for the other toxins. Tests for thimerosal, formaldehyde, aluminum, general safety, container integrity, sterility, sodium chloride, and standard detoxification test were also performed, and results were within acceptable limits and/or passed (Unpublished USAMRIID data).

As the most recent potency testing has demonstrated failure of the vaccine against toxins B, D, and E in the potency resistance to challenge, and inconclusive results or failure to all toxins to

potency antibody induction, the PBT vaccine may not be assumed to provide protection against these toxins. However, as an antibody level that correlates with protection from disease has not been established, the vaccine is still recommended to laboratory workers at risk as a component of an overall safety program for worker protection. PBT may provide some limited protection as the clinical immune response induced by the PBT vaccine may be low. Additionally, laboratory directors should review all protocols carefully to ensure safe work practices since protection to all levels of potential exposure cannot be assumed. The risk to exposure is dependent on the toxin type, the form of toxin (pure neurotoxin, partially purified, crude), and the route of exposure. It is incumbent on the Laboratory Director to determine the level of possible exposure. Unfortunately, there is little data to define the lowest level of toxin that may cause botulism symptoms. Best estimates from non-human primate studies suggest that the lethal dose for humans may be between 1 ng and 1 μg per Kg of adult weight, depending in part on the route of administration. While the common route of natural exposure is through ingestion of contaminated food products, laboratory workers may also be at risk due to accidental injection or through contamination of mucus membranes through aerosols or droplets. Safety procedures should be in place to reduce these risks.

The investigators must develop study-specific safety protocols to ensure protection of laboratory workers. The 4th Edition of the Department of Health and Human Services (HHS) Biosafety in Microbiological and Biomedical Laboratories (BMBL), U.S. Government Printing Office, Washington, 1999 is the definitive resource for safely handling all infectious and biological agents including botulinum toxin. A copy of BMBL can be obtained from http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm. An excerpt follows for handling *Clostridium botulinum* and its associated neurotoxins:

> **"***Containment recommendations:* Biosafety Level 2 practices, containment equipment, and facilities are recommended for activities that involve the organism or the toxin. Solutions of sodium hypochlorite (0.1%) or sodium hydroxide (0.1N) readily inactivate the toxin and are recommended for decontamination of work surfaces and for spills. Autoclaving of contaminated materials is also appropriate. Biosafety Level 3 containment and personnel precautions are required for activities with a high potential for aerosol or droplet production, and for those involving large quantities (> 10 L) of the organism. Animal Biosafety Level 2 practices, containment equipment, and facilities are recommended for diagnostic studies and titration of toxin."

Of the several distinct botulinum neurotoxins (A, B, C, D, E, F, G), only types A and B have been approved by the FDA for therapeutic use. Three products, botulinum toxin type A (Botox® and Botox® Cosmetic) and botulinum toxin type B (Myobloc®), have been approved by the FDA. Botox® is approved for treatment of strabismus, blepharospasm, and cervical dystonia. Botox® Cosmetic is approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age. Myobloc® is approved for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. If individuals vaccinated with PBT need or desire treatment with these approved products, they may see diminished or nonexistent clinical or therapeutic effects because of PBT's antibodies to the A and B toxins. This is a theoretical biological interaction because currently there are no documented or published cases of this interaction. There are no data showing how long these antibodies last after the last toxoid injection or how long an individual immunized with botulinum toxoid would be unable to use therapeutic botulinum toxin type A (Botox® or Botox® Cosmetic) or type B (Myobloc®).

The PBT vaccine contains thimerosal. Thimerosal is one of the most widely used preservatives in vaccines. It is believed that thimerosal poses no mercury poisoning risk to adults. Some people have local skin reactions such as redness and swelling that may suggest a delayed-type of minor allergic reaction following shots with products that have thimerosal. Research suggests that most people who have a contact or skin allergy to thimerosal will not have the reaction when thimerosal is given under the skin. If a subject has a history of minor allergic reaction to thimerosal in a vaccine in the past, a subject should be able to receive PBT. If a subject has a history of a severe allergic reaction to any vaccine in the past, then a subject should not receive PBT.

As with any vaccine administration, and no matter what precautions are taken, the risk of a serious or life-threatening allergic reaction or infection with an unknown adventitious agent exists.

The PBT vaccine has been tested in animal and cell cultures for residual toxin and adventitious agents, and none has been found. However, the risk of undetected agents cannot be completely eliminated. Possible intoxication indistinguishable from the natural disease could also occur. With botulism, the natural disease includes muscular weakness, paralysis, permanent neurologic damage, and death. To date, there have been no reported cases of botulism or encephalitis from this vaccine.

Less likely, but possible, is the theoretical chance of a vaccinee acquiring GBS. Approximately 3,500 cases of GBS are recorded per year in the United States and Canada. CDC reports that 95% of the cases are not temporally associated with the administration of vaccines; however, GBS was associated with campylobacter infections, as well as the influenza vaccine formulations in 1976, 1993, and 1994. GBS is a motor neuron disease, but sensory symptoms may occur along with radicular pain. Patients generally present with weakness and loss of lower extremity reflexes. GBS usually occurs as an ascending motor neuron process, with the lower extremities usually involved first and more severely affected than the upper extremities. The bulbar musculature may be involved as well. The death rate from GBS may be 3–4%. Approximately 85% of patients make a complete or nearly complete recovery. Management includes supportive care, plasmapheresis, and administration of high-dose immunoglobulins. No cause-and-effect relationship between vaccination with PBT and GBS has been found.

THIS VACCINE WILL NOT BE ADMINISTERED TO WOMEN WHO THINK THAT THEY MIGHT BE PREGNANT. Animal reproduction studies have not been conducted with the PBT vaccine, and this vaccine has never been tested in pregnant women. Therefore, the potential risks to pregnant women and their fetuses are unknown. Females must avoid the possibility of pregnancy at the time of vaccination and for 3 months after each vaccination. Also, it is not known if antibodies to the PBT vaccine are excreted in breast milk. Problems related to PBT vaccination in women who are breastfeeding have not been studied.

Risks to Study Personnel and the Environment

This protocol presents no hazard to study personnel other than those normally associated with routine vaccination of human subjects. The principal risks to study personnel in the clinical setting are those associated with needle sticks. The principal risks to the laboratory workers are those of working with botulinum toxins.

There are no known risks to the environment other than those associated with the generation of biohazardous wastes attendant with vaccination of humans. All biohazardous wastes will be disposed of in compliance with local, state, and federal regulations.

Benefits to Subjects
The intended benefit of administering the PBT vaccine is the induction of an immune response in subjects potentially exposed to botulinum toxins in the laboratory. It is expected that vaccination will result in antitoxin levels that provide potential protection against serotypes of botulinum toxin covered by the vaccine. However, due to recent failed or inconclusive potency studies, the vaccine must now be assumed to offer no protection against toxins A-E. Although individuals vaccinated with PBT have adequate antibodies to toxin A, and 100% of guinea pigs vaccinated with PBT survived challenge to toxin A in the potency studies, the inconclusive results of the potency antibody induction prohibits suggesting that there may be a possible benefit to toxin A at this time.

Alternatives to Vaccination
At this time, there is no known medical alternative to taking this vaccine that affords the same potential protection from botulism. An option would be not to participate in this study and hence not to work with botulinum toxins. Other types of protection used by laboratory workers performing research on botulinum toxin include physical barriers such as personal respirators or containment suits with a forced air supply. An unprotected individual involved in a serious exposure to botulism may be given equine botulinum antitoxin after such an exposure; however, supplies of this antitoxin are extremely limited.

4.0 PROTOCOL DESIGN

Investigational Plan
The PBT vaccine will be administered only to subjects at risk for botulinum toxin poisoning. At-risk subjects are those currently working with cultures of *C. botulinum* or other organisms that produce botulism neurotoxin, subjects expecting to handle preparations of botulism.

Volunteer Assignment to Treatment Group
All volunteers consenting will receive PBT.

Program Population
The program population will include at-risk laboratory workers who require protection against potential exposure to botulinum toxins and typically averages 300 persons annually.

Inclusion Criteria/Eligibility
Volunteers must meet all the following inclusion criteria to be eligible for this study:

- In good general health.
- Male or female of any race or ethnic origin.
- $\geq$ 18 years of age at time of study enrollment.
- At risk for exposure to botulinum toxins. Individuals at risk include (1) those who work with cultures of *C. botulinum* or other organisms that produce botulism neurotoxins and (2) individuals expecting to handle preparations of botulism.

Exclusion Criteria
Volunteers who present any of the following exclusion criteria will not be enrolled in the study:

- Females who are pregnant or breastfeeding during the study or who intend to become pregnant within 90 days of a scheduled vaccination.

- Females of childbearing potential who have not been surgically sterilized or are not abstaining from sexual intercourse or are not practicing an acceptable, in the opinion of the investigator, means of hormonal or barrier contraception.
- Disease or drug therapy or other therapeutic intervention (e.g., radiation therapy) that suppresses the immune system.
- History of acute allergic response to one or more components of PBT: aluminum, thimerosal, mercury, and formaldehyde.
- Administration of another vaccine (generally) within 28 days of PBT vaccination.
- A history of immunodeficiency such as subjects who test positive for human immunodeficiency virus (HIV).
- Any unresolved adverse event resulting from a previous vaccination.

5.0 PRODUCT SOURCE AND DESCRIPTION

The PBT vaccine is a combination of aluminum phosphate-adsorbed toxoid derived from formalin-inactivated, partially purified types A-E botulinum toxins. Each 5 mL multidose vial contains 0.22% formaldehyde as a stabilizer and 1:10,000 thimerosal as a preservative. Each 0.5 mL dose contains 7 mg aluminum phosphate and approximately 5 μg inactivated toxin. PBT vaccine is labeled for human administration and includes the following statement: "CAUTION: NEW DRUG—Limited by Federal law to Investigational Use." The currently distributed toxoid is manufactured by the Michigan Biologic Products Institute (MDPH), Lansing, Michigan 48909.

Quantitative composition of PBT is:

Type A toxoid - 1.7 Lf/mL[1]
Type B toxoid - 0.54 Lf per mL[1]
Type C toxoid - 50,000 $MIPLD_{50}$[2] equivalents per mL
Type D toxoid - 4 Lf/mL[1]
Type E toxoid - 0.5 Lf or 100,000 $MIPLD_{50}$[2] equivalents per mL
[1]Limits of flocculation/mL or 50% lethal dose
[2]Mouse IP 50% lethal dose

The PBT vaccine must be maintained at 2ºC to 8ºC (36ºF to 46ºF) in a designated refrigerator. The vaccine must NOT be frozen. Vials of vaccine may be refrigerated and utilized until all doses have been withdrawn.

6.0 ADVERSE EVENTS

Based on over 35 years of experience with vaccine administration by CDC under BB-IND 161, PBT appears to have an acceptable safety profile. Results of PBT vaccination from 1970 to 2008 (N=25,220) showed that 89.14% of primary and booster injections of PBT resulted in none or mild local reactions, 7.88% were moderate local reactions (edema or induration > 30 mm but < 120 mm), and 0.34% were severe local reactions (> 120 mm size reaction or any reaction accompanied by marked limitation of motion of the arm or marked axillary node tenderness) (see Table II). Systemic reactions occurred in 5.7% of the 25,220 primary or booster injections of PBT. The reactions were generally mild and consisted of soreness, fever, tiredness, headache, rashes, and muscle pain. The incidence of systemic reactions following PBT vaccination by CDC from 1970 to 2008 was as follows: general malaise occurring in 0.5%; chills, fever, or other flu-like symptoms in 0.5%; headache in 0.6%; blurred vision or dizziness in 0.3%; nausea, vomiting or diarrhea in 0.4%; itching

or hives in 1.1%; and either soreness or stiff back or neck or lumps or swelling in 2.3% of individuals (see Table III).

Table II: Incidence and Severity of Local Reactions Following PBT Vaccination, CDC Data 1970-2008 (% of 25,220 injections)

	Reactions				
	None to Mild[1]	**Moderate[2]**	**Severe[3]**	**No Response Recorded**	**Total**
Initial Series					
1	5982	185	5	117	6289
2	5477	352	9	128	5966
3	4766	434	15	141	5356
4*	276	62	-	74	412
Other primary	10	6	-	2	18
subtotal	***16,511***	***1,039***	***29***	***462***	***18,041***
Booster Injections					
1st	2807	438	29	109	3383
2nd	1194	207	12	49	1462
3rd	643	107	7	22	779
4th or more	1303	194	9	23	1529
unknown	23	2	-	1	26
subtotal	***5,970***	***948***	***57***	***204***	***7,179***
TOTAL (%)	***22,481 (89.14)***	***1,987 (7.88)***	***86 (0.34)***	***666 (2.64)***	***25,220 (100)***

*4th injection of initial series began April 2004

[1]None = No reactions; Mild = Erythema only; edema or induration that is measurable but ≤30 mm in any diameter.

[2]Moderate = Edema or induration measuring >30 mm and <120 mm in any one diameter.

[3]Severe = Any reaction measuring >120 mm in any one diameter or any reaction accompanied by marked limitation of motion of the arm or marked axillary node tenderness.

Table III. Incidence of Systemic Reactions Following PBT Vaccination, CDC Data 1970-2008 (% of 25,220 injections)

Year ending in	General Malaise	Chills, Fever, flu-like symptoms	Headache	Swelling, lumps, soreness, stiff back, neck	Blurred vision, numbness, dizziness, lighthead-edness	Nausea, diarrhea, vomiting, GI	Itching, hives, rash, edema	Total No. of systemic reactions
1970	2	7	2	1	3	5	0	20
1971	3	1	1	2	1	1	0	9
1972	6	4	6	2	0	2	0	20
1973	4	5	2	1	4	4	0	20
1974	5	9	1	3	3	3	0	24
1975	2	1	2	1	3	4	0	13
1976	0	1	0	2	1	1	0	5
1977	0	1	0	0	0	2	0	3
1978	3	0	1	2	1	0	1	8
1979	1	1	1	0	5	1	1	10
1980	1	0	1	10	0	0	4	16
1981	2	3	4	6	3	4	1	23
1982[a]	0	0	0	2	0	1	0	3
1983	0	0	0	2	1	0	0	3
1984	0	0	0	0	0	1	0	1
1985	2	0	1	12	0	1	3	19
1986	3	3	2	5	3	1	0	17
1987	5	4	4	15	1	0	7	36
1988	3	7	2	31	0	0	6	49
1989	1	0	1	32	0	0	4	38
1990	6	2	2	22	0	3	2	37
1991	2	4	6	29	1	3	12	57
1992	1	3	2	18	1	0	8	33
1993	5	6	6	27	4	6	12	66
1994[b]	8	2	2	49	0	6	3	70
1995	4	3	6	32	1	5	13	64
1996	6	1	5	13	1	4	5	35
1997	4	1	3	29	1	5	5	48
1998	12	3	7	40	2	4	15	83
1999	5	4	22	0	1	1	2	35
2000	8	7	22	21	3	9	11	81
2001	11	4	3	3	1	4	35	61
2002	13	7	18	4	4	5	40	91
2003	2	8	2	0	0	1	13	26
2004	1	5	3	38	0	1	16	64
2005	11	5	6	18	5	2	12	59
2006	4	8	1	34	3	4	12	66
2007	2	5	1	27	2	2	8	47
2008	5	8	3	64	6	7	38	131
TOTAL (%)	**142 (0.5)**	**128 (0.5)**	**145 (0.6)**	**579 (2.3)**	**60 (0.3)**	**101 (0.4)**	**277 (1.1)**	**1,432 (5.7)**

[a] Distribution of MDPH Lot A-2 began, previously only Parke-Davis & Co. product was distributed.
[b] Distribution of MDPH Lot PBP003 began.

Moderate local reactions include erythema, edema and induration. All such reactions reach a peak in 24 hours, then gradually subside and should be gone at 48 hours or at the most 72 hours. When a moderate local reaction occurs, the following 0.5 mL dose may be divided (0.25 mL each) and given

over a 2–3 day period. This has been shown to alleviate the reaction without impairing the antitoxin response.

Any serious systemic reactions or serious local reactions should be recorded on the CDC Pentavalent Botulinum Toxoid IND 161 Severe Serious Adverse Reaction Event Follow-Up Questionnaire Form (see Appendix D) and reported by telephone or FAX to the CDC Drug Service.

Recipients who develop severe local reactions may benefit from a modified administration schedule where 0.1 mL is given daily over 5 days. This administration of the total dose over several days may reduce the risk of subsequent severe local reactions.

Rarely, an individual may have a reaction characterized by a deep, painless, non-inflammatory subcutaneous induration that may persist for 3 to 4 weeks. These rarely measure more than 2 to 3 centimeters in diameter and are absorbed without residue.

Definitions of Adverse Events

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A SERIOUS ADVERSE EVENT is any untoward medical occurrence that, at any dose:

1. results in death,
2. is life threatening,
3. requires in-patient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacitation, or
5. is a congenital anomaly/birth defect.

An UNEXPECTED ADVERSE EVENT is an adverse reaction, the nature or severity of which is not consistent with the applicable product information or any AE that has not been documented previously as an event to be expected (i.e., nature, frequency, or intensity) with administration of the product.

Assessing AEs

Volunteered, observed, and elicited AEs should be recorded. These include AEs that the patient reports spontaneously, those the physician observes, and those the physician elicits in response to open-ended questions.

Intensity

Regardless of the classification of an AE as serious or not, severity must be assessed according to the following categories:

- Mild - does not interfere with daily activities
- Moderate - interferes with routine activities
- Severe - unable to perform routine activities

Recording AEs

The following information must be recorded for all AEs:

- Patient's name
- Investigator's name
- Program vaccine and dates of administration
- Date and time of onset
- Signs, symptoms, and severity

7.0 ADMINISTRATION OF PBT

SHAKE WELL before withdrawing each dose. Do not inject intracutaneously or into superficial structures. A 48 hour-post-vaccine arm examination is required following each inoculation. The first injection is represented by week 0. There is a 2-week interval between the first and second injection and a 12-week interval between the first and third injection. There is a 24-week (6 months) interval between the first and fourth injections.

Initial Vaccination Series: 0.5 mL deep subcutaneously at 0, 2, 12, and 24 weeks.

Boosters: 0.5 mL deep subcutaneously 12 months after the first injection of the initial series and yearly thereafter.

Recipients who develop severe local reactions may benefit from a modified administration schedule where 0.1ml is given daily over 5 days. This administration of the total dose over several days may reduce the risk of subsequent severe local reactions. When a moderate local reaction occurs, the 0.5mL dose may be divided (0.25 mL each) and given over a 2–3 day period.

8.0 PROTOCOL MODIFICATIONS

Any change or modification to the protocol that affects patients, objectives, design, procedures, or significant administrative aspects of the protocol will require a formal amendment. Such amendments will be agreed upon and approved by the Sponsor, the Principal Investigator, and the CDC IRB prior to any implementation of said change or modification.

Administrative changes to the protocol include corrections and/or clarifications that have no effect on the way the program is conducted. These administrative changes will be agreed upon by the Sponsor and the Principal Investigator and will be documented in the protocol file. The CDC IRB will be notified in writing of all administrative changes prior to their implementation.

9.0 PROTOCOL DEVIATIONS

Deviations are defined as isolated occurrences involving a procedure that did not adhere to the program. The Principal Investigator is responsible for identifying any program deviations. Each deviation will be recorded and placed in the patient's case report form at the protocol site.

10.0 DATA MANAGEMENT

Recording Clinical Data
The following forms will be used as source documentation:

Appendix C Response to Investigational New Drug Form

Appendix D Severe Adverse Reaction Follow-up Questionnaire Form

Appendix E Statement of Physician Form

Appendix F Investigational New Drug Accountability Form

All original case report forms will be maintained in each patient's permanent medical record.

Data Handling
Clinical data obtained during a patient's participation in the protocol will be entered into an individual medical record and a database maintained by the CDC Drug Service.

11.0 ETHICAL, LEGAL, AND ADMINISTRATIVE REQUIREMENTS

Good Clinical Practices
The procedures set forth in this protocol are designed to ensure that the Sponsor and all protocol personnel abide by the U.S. Code of Federal Regulations (CFR) and the Good Clinical Practice guidelines. The Principal Investigator acknowledges this by the Form FDA 1572.

Informed Consent
Written informed consent in compliance with 21 CFR 50 will be obtained before any protocol-related procedures are initiated. The Principal Investigator or sub-investigator will present the protocol in lay terms to the patient. Questions about the nature of the protocol, the means by which the protocol is to be conducted, and the risks to the patient will be solicited.

12.0 PROTOCOL MONITORING

A Sponsor-designated clinical monitor (CDC Drug Service) will monitor this protocol.

13.0 FINANCIAL REMUNERATION AND INSURANCE

CDC is providing PBT for this clinical protocol. Should a patient be injured as a direct result of participating in this protocol, he/she should be treated immediately; however, CDC will not pay for this treatment. The patient should understand that this does not constitute a waiver or release of legal rights. This issue is addressed in the consent form and will be discussed with the patient by the clinician.

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15.0 PROGRAM TEAM ROSTER

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Appendix A

Investigator's Brochure
Pentavalent (ABCDE) Botulinum Toxoid

Investigator's Brochure
Pentavalent (ABCDE) Botulinum Toxoid

COMPOSITION

Pentavalent (ABCDE) Botulinum toxoid Aluminum Phosphate Adsorbed is a combination of aluminum phosphate-adsorbed toxoid derived from formalin-inactivated, partially purified types A, B, C, D, and E botulinum toxins. Each vial contains 0.022% formaldehyde and 1:10,000 thimerosal as a preservative. The currently distributed toxoid is manufactured by the Michigan Biologic Products Institute Lansing, Michigan 48909.

ADMINISTRATION AND DOSAGE

SHAKE WELL before withdrawing each dose. Do not inject intracutaneously or into superficial structures. A 48 hour post vaccine arm examination is required following each inoculation. The first injection is represented by week 0. There is a 2 week interval between the first and second injection and a 12 week interval between the first and third injection. There is a 24 week (6 month) interval between the first and fourth injections.

Initial Vaccination Series: 0.5 mL deep subcutaneously at 0-2-12-24 weeks.

Boosters: 0.5 mL deep subcutaneously 12 months after the first injection of the initial series and yearly thereafter.

Recipients that develop severe local reactions may benefit from a modified administration schedule where 0.1 mL is given daily over 5 days. This administration of the total dose over several days may reduce the risk of subsequent severe local reactions. When a moderate local reaction occurs, the 0.5 mL dose may be divided (0.25 mL each) and given over a 2–3 day period.

PRECAUTIONS

1. Botulinum toxoid is not a licensed product and must be distributed as an Investigational New Drug (IND) in accordance with requirements of the U. S. Food and Drug Administration (FDA). It must be administered by or under the supervision of the physician who requested the toxoid. The physician must be enrolled as a co-investigator by completing Form FDA 1572, "Statement of Investigator" and Form CDC 3.547 "Statement of Physician". The completed forms should be returned to the CDC Drug Service (MS D-09), Atlanta, GA 30333.

2. It should be emphasized that the toxoid provides partial protection from exposure to several botulinum toxin types, and is an adjunct to good laboratory safety practices. Specifically, immunization with toxoid cannot be relied on to protect a worker in the event of exposure because: a) the target titers of protective antibody are believed to protect against exposure from clinical specimens, but not high-toxin content samples such as culture supernatant or purified toxin, b) recent data show that titers in vaccinees fall below target, and c) questions have been raised about the potency of the existing toxoid stock.

3. The toxoid should be administered only to healthy men and women, equal to or above the age of 18. The effects of administration of the toxoid during pregnancy have not been studied. The

4. Each recipient must sign a consent form, CDC 58.43. One copy is given to the recipient; one copy is maintained by the clinical investigator.

5. Form CDC 519.7, "Response to Investigational New Drug", must be completed for each recipient and returned to the CDC Drug Service.

REACTIONS

Since 1970, over 25,000 injections of the toxoid have been administered to recipients who were subsequently observed for adverse reactions. The rate of moderate and severe local reactions was 4.1% and 0.1%, respectively, for the initial series of shots and 3.8% and 0.2% for booster shots (Table I). In addition, there was a low incidence of systemic reactions (5.7%) for both the initial series and the booster shots. The systemic reactions were generally mild consisting of pain and soreness, fever, tiredness, headache, rashes, and muscle pain (Table II). Systemic reactions were often concurrent with local reactions.

Moderate local reactions include erythema, edema, and induration. All such reactions reach a peak in 24 hours, then gradually subside and should be gone at 48 hours or at the most 72 hours. When a moderate local reaction occurs, the 0.5 mL dose may be divided (0.25 mL each) and given over a 2–3 day period. This has been shown to alleviate the reaction without impairing the antitoxin response.

Any serious systemic reactions or serious local reactions should be recorded on the CDC Pentavalent Botulinum Toxoid IND 161 Serious Adverse Event Follow-Up Questionnaire Form and reported by telephone or FAX to the CDC Drug Service. Recipients that develop severe local reactions may benefit from a modified administration schedule where 0.1 mL is given daily over 5 days. This administration of the total dose over several days may reduce the risk of subsequent severe local reactions.

Rarely, an individual may have a reaction characterized by a deep, painless, non-inflammatory subcutaneous induration that may persist for 3 to 4 weeks. These rarely measure more than 2 to 3 centimeters in diameter and are absorbed without residue.

Of the several distinct botulinum neurotoxins (A,B,C,D,E,F,G), only types A and B have been approved by the FDA for therapeutic use. Three products, botulinum toxin type A (Botox® and Botox® Cosmetic*)* and botulinum toxin type B *(*Myobloc®*)* have been approved by the FDA. Botox® is approved for treatment of strabismus, blepharospasm and cervical dystonia. Botox® Cosmetic is approved for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age. Myobloc® is approved for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. If individuals vaccinated with botulinum toxoid A,B,C,D,E ever need or desire treatment with these toxins, they may see diminished or nonexistent clinical or therapeutic effects of botulinum toxin type A and B because of their antibodies to the A and B toxin. This is a theoretical biological interaction because currently there are no documented or published cases of this interaction. There are no data showing how long these antibodies last after the last toxoid injection or how long an individual immunized with

botulinum toxoid would be unable to use therapeutic botulinum toxin type A (Botox® and Botox® Cosmetic) or type B (Myobloc®).

IMMUNOGENICITY

Experience with pentavalent botulinum toxoid has shown that: (a) it has been effective in protecting animals against intraperitoneal challenge with toxins of types A, B, C, D, and E of *Clostridium botulinum*, (b) the serum antitoxin levels in animals as determined by mouse protection tests correlate with protective activity , and (c) the toxoid introduced into man has historically produced levels of antitoxin thought to be protective as judged by extrapolation of data derived from animal experiments.

In experiments with the original lot of toxoid (1,2), 30 persons were immunized on a 0–2–12 week schedule. Antitoxin titers were detectable for all 5 types of toxin in about 80% of the volunteers 2 weeks after the initial series. These titers declined during the next 12 weeks and only a small percentage had measurable titers by one year, just before the boosters were given. Eight weeks after the boosters, 100% of the recipients had measurable titers to all 5 types.

In 1988 the U.S. Army Medical Research Institute of Infectious Disease (USAMRIID) evaluated immunized individuals for neutralizing antibodies to type A & B botulinum toxins. After the primary series, 91% of subjects had a type A titer $\geq$ 0.08 IU/mL, and 78% of subjects had a type B titer $\geq$ 0.02 IU/mL. After the first booster all individuals tested had a demonstrable titer for type A & B (3).

SUPPLIER

The toxoid is supplied by the Centers for Disease Control, Atlanta, Georgia. Inquiries for toxoid or forms required for inoculation should be directed to:

Centers for Disease Control and Prevention
Drug Services
1600 Clifton Rd; Mailstop D-09
Atlanta, Georgia 30333
Phone: 404-639-3670
FAX: 404-639-3717

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Table I: Incidence and Severity of Local Reactions Following PBT Vaccination, CDC Data 1970-2008 (% of 25,220 injections)

	Reactions				
	None to Mild	**Moderate**	**Severe**	**No Response Recorded**	**Total**
Initial Series					
1	5982	185	5	117	6289
2	5477	352	9	128	5966
3	4766	434	15	141	5356
4*	276	62	-	74	412
Other primary	10	6	-	2	18
Subtotal	***16,511***	***1,039***	***29***	***462***	***18,041***
Booster Injections					
1st	2807	438	29	109	3383
2nd	1194	207	12	49	1462
3rd	643	107	7	22	779
4th or more	1303	194	9	23	1529
unknown	23	2	-	1	26
subtotal	***5,970***	***948***	***57***	***204***	***7,179***
TOTAL (%)	***22,481 (89.14)***	***1,987 (7.88)***	***86 (0.34)***	***666 (2.64)***	***25,220 (100)***

4th injection of initial series began April 2004
None = No reactions.
Mild = Erythema only; edema or induration that is measurable but ≤30 mm in any diameter.
Moderate = Edema or induration measuring >30 mm and <120 mm in any one diameter.
Severe = Any reaction measuring >120 mm in any one diameter or any reaction accompanied by marked limitation of motion of the arm or marked axillary node tenderness.

Table II: Incidence of Systemic Reactions Following PBT Vaccination, CDC Data 1970-2008 (% of 25,220 injections)

Year ending in	General Malaise	Chills, Fever, flu-like symptoms	Headache	Swelling, lumps, soreness, stiff back, neck	Blurred vision, numbness, dizziness, lighthead-edness	Nausea, diarrhea, vomiting, GI	Itching, hives, rash, edema	Total No. of systemic reactions
1970	2	7	2	1	3	5	0	20
1971	3	1	1	2	1	1	0	9
1972	6	4	6	2	0	2	0	20
1973	4	5	2	1	4	4	0	20
1974	5	9	1	3	3	3	0	24
1975	2	1	2	1	3	4	0	13
1976	0	1	0	2	1	1	0	5
1977	0	1	0	0	0	2	0	3
1978	3	0	1	2	1	0	1	8
1979	1	1	1	0	5	1	1	10
1980	1	0	1	10	0	0	4	16
1981	2	3	4	6	3	4	1	23
1982[a]	0	0	0	2	0	1	0	3
1983	0	0	0	2	1	0	0	3
1984	0	0	0	0	0	1	0	1
1985	2	0	1	12	0	1	3	19
1986	3	3	2	5	3	1	0	17
1987	5	4	4	15	1	0	7	36
1988	3	7	2	31	0	0	6	49
1989	1	0	1	32	0	0	4	38
1990	6	2	2	22	0	3	2	37
1991	2	4	6	29	1	3	12	57
1992	1	3	2	18	1	0	8	33
1993	5	6	6	27	4	6	12	66
1994[b]	8	2	2	49	0	6	3	70
1995	4	3	6	32	1	5	13	64
1996	6	1	5	13	1	4	5	35
1997	4	1	3	29	1	5	5	48
1998	12	3	7	40	2	4	15	83
1999	5	4	22	0	1	1	2	35
2000	8	7	22	21	3	9	11	81
2001	11	4	3	3	1	4	35	61
2002	13	7	18	4	4	5	40	91
2003	2	8	2	0	0	1	13	26
2004	1	5	3	38	0	1	16	64
2005	11	5	6	18	5	2	12	59
2006	4	8	1	34	3	4	12	66
2007	2	5	1	27	2	2	8	47
2008	5	8	3	64	6	7	38	131
TOTAL (%)	**142 (0.5)**	**128 (0.5)**	**145 (0.6)**	**579 (2.3)**	**60 (0.3)**	**101 (0.4)**	**277 (1.1)**	**1,432 (5.7)**

[a] Distribution of MDPH Lot A-2 began, previously only Parke-Davis & Co. product was distributed.
[b] Distribution of MDPH Lot PBP003 began.

Appendix B

Consent Form
Pentavalent (ABCDE) Botulinum Toxoid

CONSENT FORM
Botulinum Toxoid Adsorbed
Pentavalent (ABCDE)

Revised October 2009
Flesch-Kincaid Grade Level 8.8

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of the study is to give Botulinum Toxoid Adsorbed Pentavalent (PBT) vaccine to people who are at risk of exposure to botulinum toxin at work. If you are exposed to botulinum toxins at work, the PBT vaccine may lower the risk of you getting botulism.

BACKGROUND:

Botulism is a very serious illness. If you have it, it may cause weakness, dry mouth, and loss of your nerve function. A toxin made by a bacterium causes the disease. If a person eats or drinks, inhales, or injects the toxin, it will bind to a certain area of a nerve and stop the transfer of the nerve signal to the muscles. This will usually cause blurred vision, drooping of the eyelids, trouble swallowing, trouble speaking, and muscle weakness leading to being unable to move and/or death. Death may occur because the muscles needed for breathing stop working. With modern treatment, less than 5% of botulism patients die.

The PBT vaccine is used for people who are at risk of getting botulism from the botulism toxins made by the bacterium. A toxoid is a type of vaccine that is made when a toxin is changed so that it no longer causes disease. When the vaccine is given, the body makes antibodies that protect you against the toxin. The PBT vaccine contains small amounts of formaldehyde and thimerosal as a preservative.

The PBT vaccine is not a licensed product in the United States. The Food and Drug Administration (FDA) allows the Centers for Disease Control and Prevention (CDC) to supply the PBT vaccine under rules that apply to investigational drugs. This means that your doctor must enroll with CDC and must keep records on every dose given. CDC has been giving the PBT vaccine under a research study since 1967. This study has given important public health facts on the vaccine.

If you agree to get the PBT vaccine, you will need to get a few vaccine shots so that your body can make enough antibodies to protect you in case you are exposed to the toxin. You will get the first shot, and then 2 weeks later you will get a second shot. A third shot is given 12 weeks after your first. A fourth shot will be given 24 weeks after your first. These first four shots are called the initial series. A booster is given 12 months after the first shot of the initial series and yearly thereafter. Your doctor or nurse will need to check your arm 48 hours after each shot to see if you are having any reaction to the vaccine. Over 90% of people who got the vaccine initial series and one booster had enough antibodies to protect them from botulism.

ARE THERE ANY RISKS?

Vaccine Not Working As Well

The PBT vaccine was manufactured in the 1970's and is tested once a year to see how it works. The results of recent testing showed that the vaccine might not work as well as it has in the past against all strains of botulism toxin. It is possible that these results may have been due to problems in doing the testing because these types of tests are hard to do.

It is important to know that the vaccine is used to help protect against the botulism toxins, but other personal protective measures are still required. You should think of personal protective measures as the only protective measure against any of these bacteria toxins at this time.

Side Effects

Response forms received between 1970 to 2008 showed that about 8.2% of 25,220 vaccine shots had moderate or severe reactions at the shot site. Usually this is redness only, but swelling may be seen. About 5% of people had one or more of the following: pain and soreness; itching; tiredness; fever and/or chills; headache; sore joints and stiff neck; dizziness; nausea, or vomiting; double vision; prickling feeling on face and body; and rash. You should tell your doctor about any side effects or problems that you think were caused by the vaccine.

You should tell your doctor if you are enrolled in another research study.

For Patients Receiving Botox® or MyoBloc® Therapy

The FDA allows botulinum toxin types A and B to be used as medicines. Botulinum toxin type A (Botox®) and botulinum toxin type B (MyoBloc®) are used to help with odd head position and neck pain caused by cervical dystonia. Cervical dystonia is a disease where you are not able to control the movements of your neck muscles and/or the position of your head and neck. Botox® is also used to treat other muscle problems and to get rid of wrinkles. The PBT vaccine helps your immune system fight the effects of these toxins A and B. Getting the PBT vaccine might keep Botox® and MyoBloc® from working if you need these drugs in the future. Right now, there are no facts about how long your body would fight these drugs or if it would fight them at all. If you are getting Botox® or MyoBloc® therapy right now, you should think carefully about being in this study.

Guillain-Barré Syndrome
It is not known whether you can get Guillain-Barré syndrome (GBS) if you take the PBT vaccine. GBS is a disease in the nerves that help you to move. Loss of being able to feel objects, numbness or tingling feelings along with nerve pain may also occur with this disease. The death rate from GBS may be 3%–4%. About 85% of patients with GBS get better. Right now, there is no proof that the PBT vaccine causes GBS. There have been no reported cases of GBS from people vaccinated with the PBT vaccine.

Pregnancy
The use of this vaccine during pregnancy has not been studied. Possible side effects of the vaccine, including fever and allergic or toxic reaction, might affect a developing fetus. Further, if by accident the vaccine should contain any live toxin, it might result in unknown but large risks of defects or death to the unborn baby. Therefore, if you are female, you should not receive this vaccine if pregnant. The only ways to avoid any risks to the unborn baby are (1) do not become pregnant; or (2) do not get vaccinated. You should not become pregnant for 3 months after vaccination; therefore, if you are female, you should use reliable birth control during this period. Birth control pills and injectable, implantable, or insertable hormonal birth control products work best. However, any single form of birth control can fail. Other birth control methods such as use of a condom, diaphragm, IUD, or sperm killing product can be used with these hormone products to help them to work better.

Thimerosal
The PBT vaccine contains thimerosal. Thimerosal is one of the most widely used preservatives in vaccines. It is not believed that thimerosal poses a mercury poisoning risk to adults. Some people have local skin reactions such as redness and swelling that may suggest a delayed-type of minor allergic reaction following shots with products that have thimerosal. Research suggests that most people who have a contact or skin allergy to thimerosal will not have the reaction when thimerosal is given under the skin. If you have had a minor allergic reaction to thimerosal in a vaccine in the past, you should be able to take a vaccine that contains thimerosal. If you have had a severe allergic reaction to any vaccine in the past, then you should not take the PBT vaccine.

Unknown Risks
As with all research, there is a slight chance that there are some risks we do not know about.

ARE THERE ANY BENEFITS?

This is an investigational product and getting the vaccine may not benefit you directly. The results of the most recent tests done on the PBT vaccine show that it may not work as well as it has in the past. Since 1970, there have been no reported cases of botulism from over 3,000 people vaccinated. However, you must think of personal protective measures as your only protection from botulinum toxins.

WHAT OTHER CHOICES DO YOU HAVE?

There are no other choices of vaccine for botulism at this time.

Other current types of protection used by laboratory workers who do research on botulinum toxins include physical barriers such as personal respirators or containment suits with a forced air supply. An unprotected person involved in a serious exposure to botulism may be offered an investigational

product called botulinum equine (horse) antitoxin. However, supplies of the antitoxin are extremely limited, and the antitoxin can cause serious allergic reactions.

IMPORTANT NEW FINDINGS:

You will be informed of any important new findings affecting volunteers in the study. The way we notify you will be based, in part, upon the type of information being reported.

WHAT IF I AM INJURED OR HAVE QUESTIONS?

CDC supplies the PBT vaccine free of charge. If you are hurt as a result of being in this study, treatment will/will not be provided by_____. CDC/this institution does not normally pay for harm done to you as a result of being in a research study. Thus, you (or your insurer, Medicare, or Medicaid) will have to pay for any care that is needed. However, by signing this consent form and agreeing to be in this study, you are not giving up any of your rights. If you are injured or have questions about your participation in this program, please call CDC's Deputy Assistant Director for Science at 1 (800) 584-8814. Please leave a message that includes your name and phone number with area code. Say that you are calling about CDC IRB Protocol #392. A program staff member will call you back as soon as possible. In addition, you may contact your occupational clinic, or employee health clinic at: _____ *(institution and telephone numbers)* with any questions or concerns.

You should know that CDC has certain laws and rules to follow in giving this vaccine to you. This means that your doctor must give CDC a report of your response to the vaccine. CDC will then include this data in an annual report to the FDA. This is to ensure that CDC is tracking the safety of the vaccine. If you had a reaction to the vaccine and went to the hospital, your doctor may send a copy of this hospital record to CDC. FDA and the company that makes the vaccine are allowed to look at patient files kept by CDC. If you write to CDC, we will be happy to tell you about each time we gave out your name and why. You should know that we would not use your name when we publish any facts about the use of this vaccine.

CONSENT:

I have read this form. The risks and benefits were explained to me, and I had a chance to get answers for any questions I had.

Date_____

Signature_____

Name_____
(Please Print)

Address _____

Telephone Number_____

Date_____

Investigator's Signature_____

Investigator's Name_____
(Please Print)

Address _____
(City) (State) (Zip)

Telephone Number_____

CDC IRB PROTOCOL #392

Appendix C

Response to Investigational New Drug Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL
Coordinating Center for Infectious Diseases
DRUG SERVICES D09
ATLANTA, GEORGIA 30333

RESPONSE TO INVESTIGATIONAL NEW DRUG

INSTRUCTIONS: Complete this form for each individual who receives the initial series and return it to us following the fourth injection. Complete this form for each individual who receives a booster injection and return it to us following the injection. Report a severe local reaction or a moderate or severe systemic reaction by telephone (FAX 404-639-3717) or air mail to the above address.

NAME OF RECIPIENT (Last) (First) (Middle)	AGE	SEX

OCCUPATION

RACE/ETHNICITY: (CHECK ALL THAT APPLY) ~ HISPANIC/LATINO ~ WHITE ~ BLACK ~ ASIAN ~ AM IND/ALASKA NATIVE ~ HAWAIIAN/PACIFICISLANDER

REASON FOR INOCULATION

INITIAL SERIES	NO.	DATE OF INOCULATION	Classify local reactions at 48 hours as follows:* NONE/MILD/ MODERATE/ SEVERE	ADDITIONAL REMARKS
	1			
	2			
	3			
	4			
BOOSTER (Indicate whether 1st, 2nd,3rd,etc.)				

*(Make measurements in 2 diameters perpendicular to each other.)

None -No reaction
Mild -Erythema only;edema or induration which is measurable but 30 mm or less in any one diameter
Moderate -Edema or induration measuring greater than 30 mm and less than 210 mm in any one diameter
Severe -Any reaction measuring more than 210 mm in any one diameter or any reaction accompanied by marked limitation of motion of the arm or marked axillary node tenderness

IF A MILD SYSTEMIC REACTION OCCURS, DESCRIBE BELOW:

Signature of M.D.	Print Last Name	Date

DRUG: PENTAVALENT ABCDE BOTULINUM TOXOID ALUMINUM PHOSPHATE ADSORBED

LOT NO; _____

CDC 519.7 REV. 11-03

Protocol No. 392

Appendix D

Severe Adverse Event Reaction Follow-up Questionnaire

PENTAVALENT BOTULINUM TOXOID (IND-161)
SEVERE ADVERSE REACTION FOLLOW-UP QUESTIONNAIRE

Physician Co-investigator_____

Patient Name_____

1. Previous experience with botulinum toxoid immunization. Please note dates of immunization, dose, type and extent of reaction.

2. Has the patient any known allergies, particularly to formalin or Thimerosal (Merthiolate)?

3. Has the patient experienced reactions to other immunizations? If known, which immunization(s), type of reaction(s).

4. Has the patient completely recovered from his/her reaction? If not, please note sequelae.

5. Did the patient have an unusually prolonged recovery period (longer than 10 days)? If yes, how long?

6. Was the patient physically incapacitated to the extent that he/she was unable to perform his/her normal duties? If yes, how long was he/she incapacitated?

7. Has the patient received any additional inoculations of Pentavalent Botulinum Toxoid? If so, what dose was given and what reaction was noted?

8. Describe in detail the manner in which the patient is exposed to *Clostridium botulinum* toxins.

9. Additional comments:

_____ _____

(Signature) (Date)

Appendix E

Statement of Physician Form

REQUEST FOR BOTULINUM TOXOID
STATEMENT OF PHYSICIAN

Physician:_____
(First) (Middle) (Last)

Clinic Name:_____

Number and Street:_____

City:_____**State:**_____**Postal Code:**_____**Country**_____

Telephone: ( )_____ **FAX: ( )**_____

Head of the Laboratory doing research with toxin:_____

Institute of that individual, if other than above:_____

Number and Street:_____

City:_____**State:**_____**Postal Code:**_____

Telephone:( )_____**FAX:( )**_____

Reasons for Using Botulinum Toxoid:_____

_____

_____

Name, age, position (e.g. research associate, virologist, etc.) and duties which could cause exposure of this individual to the virus used in this research project: (If more space is needed attach extra sheet)

Name	Age	Position-Duties
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Approximate Number of Recipients: Initial Series____ Initial Booster_____ Subsequent Boosters_____

THE UNDERSIGNED RECOGNIZES THAT THE FOLLOWING CONDITIONS, APPLICABLE TO NEW DRUGS FOR INVESTIGATIONAL USE, GOVERN HIS/HER RECEIPT AND USE OF THIS DRUG

A. The supplier of the drug, Scientific Resources Program, Centers for Disease Control, has made available to the physician information on prior investigations and experience, possible hazards, contraindications, side-effects, and precautions.

B. The Physician will complete the Response to Investigational Vaccine form(s), which will be made available by the supplier of the drug.

C. The physician will return the form(s) to the supplier of the drug at the specified times. Any adverse effect that may be regarded as caused by the new drug shall be reported to the supplier promptly. If the adverse effect is alarming, it shall be reported immediately.

D. The physician certifies that the drug will be administered only by individuals under his supervision.

E. The physician will inform all recipients that the drug is limited to investigational use and obtain their consent before administration.

PHYSICIAN'S SIGNATURE:_____**Date**_____

Return To: Centers for Disease Control and Prevention (CDC), Drug Service (D09), 1600 Clifton Rd., Atlanta, GA 30333, USA
Telephone: (404)639-3670 FAX: (404)639-3717 E-Mail: CDougherty@.cdc.gov , CAllen1@cdc.gov, or LEvans2@cdc.gov

CDC 3.547 Revised: 11/03

Appendix F

Accountability Form
Pentavalent (ABCDE) Botulinum Toxoid

INVESTIGATIONAL NEW DRUG (IND)
ACCOUNTABILITY FORM

Instructions: An inventory of vaccine stored at your facility is required every 12 months. If any individual has been vaccinated during the last 12 months a completed response form and consent form must be returned along with the inventory form to:

Centers for Disease Control
Drug Service D09
1600 Clifton Rd
Atlanta, GA 30333

DATE OF THIS INVENTORY_____

Name of Product:_____ Lot Number:_____

Date(s) Received:_____ Volume:_____

Date(s) Administered:_____ Volume:_____

_____ _____

Volume Remaining in Storage:_____Volume Destroyed:_____

Total Number of Initial Series Injections Administered:_____

Total Number of Booster Injections Administered:_____

Total Number of Recipients:_____

Comments:_____

_____

_____

_____

Investigator's Name (Print)

_____

Signature of Individual Doing Inventory

_____

Institution's Name

_____

City , State, Country

CDC 61.7 7/82

CDC/NCID/SRP/DRUG SERVICE/IND_ACCT_FRM.WPD