SUMMARY BASIS OF APPROVAL
Botulism Immune Globulin Intravenous (Human) (BIG-IV)

I. GENERAL INFORMATION

Submission Tracking Number:	125034.0
Biological Product Name:	Botulism Immune Globulin Intravenous (Human) (BIG-IV)
Manufactured for:	California Department of Health Services
Manufactured by:	Massachusetts Public Health Biologic Laboratories and Cangene Corporation
Trade name:	BabyBIG®

II. INDICATIONS FOR USE

BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV) is indicated for the treatment of patients below one year of age with infant botulism caused by toxin type A or B.

BabyBIG® has been tested for safety and efficacy in patients less than one year of age. BabyBIG® has not been tested for safety or efficacy in other pediatric, adult, or geriatric populations.

Animal reproduction studies have not been conducted with BabyBIG®; therefore it is not known whether BabyBIG® can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

III. DOSE FORM, ROUTE OF ADMINISTRATION AND RECOMMENED DOSAGE

A. Dose Form

BabyBIG® is supplied in a single-dose, 6-mL vial containing approximately 100 mg ± 20 mg lyophilized immunoglobulin (containing neutralizing antibody to botulinum toxins type A and type B) for reconstitution with 2 mL Sterile Water for Injection USP. Each vial contains approximately 5% gamma globulin (primarily IgG and trace amounts of IgA and IgM), 1% normal serum albumin, and 5% sucrose in 0.02 M sodium phosphate buffer. BabyBIG® is greater than 90% pure IgG. Potency (as determined by a mouse toxin neutralization assay) is greater than or equal to 15 IU/mL anti-type A toxin activity and greater than or equal to 4 IU/mL anti-type B toxin activity. BabyBIG® contains no preservative.

B. Route of Administration

After reconstitution in sterile water, BabyBIG® is administered by intravenous infusion. Approximately a 30-minute interval should be allowed for reconstitution, and BabyBIG® should be inspected visually for particulate matter and discoloration before administration. BabyBIG® should only be infused if it is colorless, free of particulate matter, and not turbid.

Infusion should begin within 2 hours after reconstitution is complete and should be concluded within 4 hours of reconstitution. Vital signs should be monitored continuously during infusion. BabyBIG® should be administered intravenously using low-volume tubing and a constant infusion pump (i.e., an IVAC pump or equivalent) at an infusion rate of 0.5 cc per kilogram body weight per hour (25 mg/kg/hr). If no untoward reactions occur after the initial 15 minutes, the rate may be increased to a maximum infusion rate of 1.0 cc/kg/hr (50 mg/kg/hr). At the recommended rates, infusion of the indicated dose takes 67.5 minutes.

Predilution of BabyBIG® before infusion is not recommended. The product should be administered through a separate intravenous line. If this is not possible, it may be "piggybacked" into a preexisting line if that line contains either Sodium Chloride Injection USP, or one of the following dextrose solutions (with or without NaCl added): 2.5% dextrose in water, 5% dextrose in water, 10% dextrose in water, or 20% dextrose in water. If a pre-existing line must be

used, BabyBIG® should not be diluted more than 1:2 with any of the above-named solutions. Admixtures of BabyBIG® with any other solutions have not been evaluated. Use of an in-line or syringe-tip sterile, disposable filter (18 µm) is recommended for the administration of BabyBIG®.

Minor adverse reactions experienced by patients treated with IGIV products have been related to the infusion rate. If the patient develops a minor side effect (e.g., flushing), the rate of infusion should be slowed or temporarily interrupted. If anaphylaxis or a significant drop in blood pressure occurs, the infusion should be discontinued and epinephrine administered.

C. Recommended Dosage

The recommended total dosage of BabyBIG® is 1mL/kg (50mg/kg), given as a single intravenous infusion as soon as the clinical diagnosis of infant botulism is made. BabyBIG® should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to, those with diabetes mellitus, volume depletion, paraproteinemia, sepsis, or those who are receiving known nephrotoxic drugs).

IV. MANUFACTURING AND CONTROLS

A. Manufacturing

Immunoglobulin is isolated from the plasma of donors immunized with pentavalent (ABCDE) botulinum toxoid. Plasma from these donors is screened for neutralizing antibodies to type A and type B botulinum toxins, and selected plasma units are pooled at the Massachusetts Public Health Biologic Laboratories (MPHBL; Jamaica Plain, Massachusetts). The pooled plasma is then fractionated by cold ethanol precipitation of the proteins according to Cohn Method 6 and Oncley Method 9 to isolate IgG. The immunoglobulin is then subjected to ultrafiltration and concentrated to at least 4.5% protein.

After ultrafiltration, the bulk immunoglobulin is filtered through a 75-nm filter and two 35-nm filters connected in series for virus removal. The bulk immunoglobulin is treated with 1% Triton X-100 and 0.3% tri-n-butyl phosphate to inactivate enveloped viruses. The mixture is filtered, stirred for at least

4 hours, and then passed through a hydrophobic chromatography column to remove the solvent and detergent. The virally inactivated globulin is formulated by adding sucrose (to 5%) and albumin (to 1%) to the IgG solution. The final bulk material is transferred to Cangene Corporation (Cangene; Winnipeg, Manitoba, Canada), where it is sterile-filtered into a filling tank, filled into 6-mL USP Type I glass vials, and lyophilized. The fill volume is calculated based on the IgG concentration and potency of the bulk material. After lyophilization, the vials are stoppered and capped at Cangene and then returned to MPHBL, where they are labeled and packaged.

Final product release tests are performed on every lot of BabyBIG®. The following tests are performed: sterility (21 CFR §610.12); IgG purity by electrophoresis; IgG and albumin protein concentration; heat stability (21 CFR §640.101); pH; prekallikrein activator activity; kallikrein activity; molecular size by high performance liquid chromatography; potency; hepatitis B surface antigen and antibody contents; anticomplementary activity; pyrogen (21 CFR §610.13b); isoagglutinins content; Anti-D content; visual appearance; residual moisture; identity; and general safety (21 CFR §610.11).

All final container lots met the requirements of 21 CFR 610 et seq. for potency, safety, sterility, purity, and identity, as well as the established specifications for BabyBIG®.

B. Validation

1. Validation of Systems, Processes, and Equipment

Utility systems, manufacturing equipment, manufacturing processes, and analytical methodologies used in the production of BabyBIG® have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

The tests performed on the bulk material and final product, as well as in-process testing, are performed according to standard operating procedures (SOPs) at MPHBL and Cangene. These testing procedures and results are documented in the batch records. The mouse toxin neutralization assay used to determine

potency and identity was validated by and is performed at Battelle Medical Research and Evaluation Facility (Battelle; Columbus, Ohio).

2. Viral Inactivation/Removal Studies

Several steps in the manufacturing process have been validated for their ability to inactivate or remove viruses that may not have been detected in the Source Plasma. These include Cohn/Oncley fractionation (Fraction I through Supernatant III Filtrate); nanofiltration through one 75-nm and two 35-nm filters; and solvent/detergent viral inactivation. These viral reduction steps have been validated in a series of *in vitro* experiments for their capacity to inactivate and/or remove Human Immunodeficiency Virus type 1 and the following model viruses: bovine viral diarrhea virus (BVDV) as a model for hepatitis C virus; mouse encephalomyelitis virus (MEMV) as a model for hepatitis A virus; and pseudorabies virus (PRV), feline calicivirus (FCV), and Sindbis virus to cover a wide range of physicochemical properties in the model viruses studied. Total mean $\log_{10}$ reductions range from 6.07 to greater than 16 $\log_{10}$, as shown in Table 1.

Table 1. Overall Viral Reduction ($\log_{10}$) in BIG-IV Manufacturing Process

	Mean Reduction Factor ($\log_{10}$)					
	Enveloped Viruses (size in nm)				**Non-Enveloped Viruses (size in nm)**	
Process Step	**Sindbis (60-70)**	**HIV-1 (80-100)**	**PRV (120-200)**	**BVDV (40-60)**	**MEMV (22-30)**	**FCV (35-39)**
Cohn/Oncley fractionation	6.6	> 9.44	> 10.37	6.25	4.06	Not done
Nanofiltration	= 6.84	Not done	Not done	= 5.4	Not done	= 6.92
Solvent/detergent treatment	Not done	> 4.51	> 5.53	> 4.85	0.57*	Not done
Cumulative Reduction Factor ($\log_{10}$)	= 13.44	> 13.95	> 15.9	= 16.5	4.63	= 6.92

* Included hydrophobic chromatography after solvent/detergent treatment.

Additional testing performed with bovine parvovirus (as a model for parvovirus B19) showed a mean cumulative reduction factor of greater than 7.34 $\log_{10}$ for Cohn/Oncley fractionation and solvent/detergent treatment followed by hydrophobic chromatography. A mean cumulative reduction factor of 2.55 $\log_{10}$ was observed for removal of porcine parvovirus by nanofiltration.

No testing or purification validation has been carried out for bovine spongiform encephalopathy (BSE). Neither bovine components nor bovine serum albumin is used in the manufacturing process. Thus, the possibility of introducing BSE into the BabyBIG® manufacturing process is considered to be negligible.

C. Stability

The sterile bulk material can be stored at 2º to 8ºC in the bulk tank for 104 days from the date of sterile filtration.

BabyBIG® is stored at 2º to 8ºC. Stability testing is performed at 3-month intervals for the first year after manufacture and then at 6-month intervals, according to the product stability program. Both lots of BabyBIG® manufactured to date have been or are being tested according to stability testing protocols. Lot 1 was manufactured in 1991 and remained stable for more than 8 years (102 months). All tests were within original specifications, except for one out-of-specification anticomplementary activity test result at 87 months; however, this out-of-specification result was not reproducible. Lot 2 was manufactured in 2000 and has remained stable for more than 3 years. BabyBIG® was also tested after incubation at 24º to 28ºC for up to 6 months (Lot 2 only) or at temperatures from -25º to 56ºC for 1 week (Lot 1 and Lot 2). All accelerated stability test results met specifications. These data support an expiration date of 24 months from the date of bulk sterile filtration for BabyBIG® when maintained at 2º to 8ºC.

No formal studies of the reconstituted drug product have been performed to determine its stability at room temperature. Nevertheless, in order to ensure aseptic use, administration of BabyBIG® should begin within two (2) hours after reconstitution is complete, and the infusion should be concluded within 4 hours of reconstitution.

D. Labeling

The product labeling consists of a physician package insert (full prescribing information), vial labels, and unit cartons. The package insert, container (vial), and package (unit carton) labels are in compliance with 21 CFR Part 201, Subparts A and B, and 21 CFR §610.60, §610.61 and §610.62. The trade name, BabyBIG®, is not known to be in conflict with or easily confused with the

trademark of any other licensed pharmaceutical product. The United States Patent and Trademark office issued a Notice of Allowance for this trade name on 07 August 2001.

E. Establishments

A prelicense establishment inspection of the MPHBL facility (Jamaica Plain, Massachusetts; U.S. License No. 64) was conducted on 08 to 11 April 2002. A prelicense establishment inspection of the Cangene facility (Winnipeg, Manitoba, Canada; U.S. License No. 1201) was conducted on 29 April to 01 May 2002. A prelicense establishment inspection of the California Department of Health Services (CDHS; Berkeley, California) was conducted on 08 to 10 May 2002.

A Form FDA 483 was issued at each location for each inspection. The facilities responded to all observations, and their corrective actions were found to be adequate and complete. All three establishments were found to be in compliance with current Good Manufacturing Practices standards. Copies of the inspection reports and the inspectional closeout memoranda are on file.

F. Environmental Assessment

A categorical exclusion from the requirement to prepare an Environmental Assessment was requested under 21 CFR §25.31(c). This request was found by FDA to be justifiable.

V. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

No nonclinical studies were conducted during the development of BabyBIG®.

VI. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

Traditional pharmacokinetic studies of BabyBIG® were not performed. However, the serum titers of the anti-A component of BabyBIG® was measured at intervals after administration. The anti-A titer data are shown in Table 2.

Table 2. BabyBIG® Anti-A Titers in Patient Sera

Time	BabyBIG Lot 1 Anti-A Titer (mean ± S.D.)	BabyBIG Lot 2 Anti-A Titer (mean ± S.D.)
	mIU/mL	
Day 1	Not done	537.1 ± 213.4
Week 2	106.7 ± 44.6	192.2 ± 71.2
Week 4	90.0 ± 39.2	155.5 ± 56.7
Week 8	54.9 ± 22.8	96.0 ± 33.2
Week 12	26.0 ± 20.5	61.4 ± 32.3
Week 16	15.6 ± 10.4	33.0 ± 22.3
Week 20	7.6 ± 6.6	19.3 ± 14.1

Half-lives of the anti-A and anti-B components of BabyBIG® were determined on the basis of serum titer data. The half-life of the anti-type A component of BabyBIG® was determined to be approximately 24.7 to 31.0 days. The half-life of the anti-B component of BabyBIG® was approximately 27.9 days.

VII. CLINICAL MICROBIOLOGY

No clinical microbiology evaluation was performed for BabyBIG® because it is not indicated as an anti-infective product.

VIII. CLINICAL SUMMARY

A. Overview

The efficacy of BabyBIG® was tested in one randomized, double-blind, placebo-controlled clinical trial (RCT) (129 patients; 122 with laboratory-confirmed infant botulism) and in three open-label studies (OLS) (144 patients). The three open-label clinical trials consisted of the following: (1) 33 patients treated with BabyBIG® under compassionate use, (2) 38 patients treated under Emergency Investigational New Drug Applications, and (3) 73 patients treated in a study conducted under Treatment IND 7776. The safety of BabyBIG® was also tested in the RCT and the OLS. Safety data for an additional 149 Treatment IND patients were submitted in the safety update.

The RCT was conducted in hospitals throughout the state of California as a multisite study. The eligible study population consisted of all patients with suspected infant botulism in California. The study design specified that 60 patients receive BabyBIG® and that a control group of 60 patients receive

placebo. The study's therapeutic intervention was a single intravenous infusion of 1 mL of clinical trial material (CTM) per kg of body weight (i.e., 50 mg/kg of body weight).

After discharge from the hospital, patient's hospital charts (shadow charts) were obtained. Before unblinding the study, efficacy and safety data were extracted from patient's shadow charts to a case report form specifically designed for the study. The primary efficacy variable of the RCT was the length of hospital stay. The secondary efficacy variables were the following:

- Length of stay in the intensive care unit
- Duration of mechanical ventilation
- Duration of tube feedings
- Cost of hospital stay, adjusted for inflation
- Number of adverse events (AEs)

Statistical testing entailed a comparison of mean values of the efficacy results by use of the t-test and a comparison of the distribution of the efficacy results by the non-parametric Kolmogorov-Smirnov (K-S) test.

The OLS were without a comparator arm, but utilized the same primary endpoint, dosage regimen, and data collection methodology as the RCT. However, in the OLS the eligible study population consisted of all patients with suspected infant botulism in the United States, with the exception of the compassionate use patients where enrollment was limited to suspected infant botulism patients within California. In addition, the OLS did not evaluate the secondary efficacy variables that were evaluated in the RCT.

B. Safety

The safety summaries and analyses of AEs in the RCT and OLS are based on the safety population, which was defined as all patients enrolled in the clinical trials.

In the RCT, 31% of BabyBIG®-treated patients experienced a treatment-emergent adverse event (TEAE) during or after treatment compared with 45% of placebo-treated patients. A substantially lower percentage of patients overall experienced a TEAE within 24 hours of CTM administration: 11% of BabyBIG® -treated patients versus 9% of placebo-treated patients. The only TEAE considered possibly related to BabyBIG® was an erythematous rash: 14% of BabyBIG®-treated patients experienced a treatment-emergent erythematous rash, as compared with 8% of placebo-treated patients ($p = 0.397$). Six percent of BabyBIG®-treated patients experienced erythematous rash within 24 hours of dosing, as compared with 0 placebo-treated patients ($p = 0.119$).

Other common TEAEs included anemia, otitis media, urinary tract infections, hyponatremia, pneumonia, and respiratory arrest. All of these TEAEs except otitis media occurred more frequently in the placebo-treated patients than in the BabyBIG®-treated patients. Otitis media occurred in 11% of BabyBIG®-treated patients during or after treatment as compared with 8% of placebo-treated patients. Anemia, pneumonia, and hyponatremia occurred slightly more frequently in BabyBIG®-treated patients within 24 hours of CTM administration, compared with the frequency of their occurrence in placebo-treated patients.

There was no evidence of anaphylaxis in any patient enrolled in the study. No patient experienced bronchospasm or anaphylactic respiratory arrest, and no patient died during BabyBIG® infusion.

Throughout the study, serious adverse events (SAEs) occurred infrequently, and when they did occur, they occurred more frequently in placebo-treated patients than in BabyBIG®-treated patients. No SAEs occurred in the study that required withdrawal of CTM, and none were considered related to BabyBIG®. AEs that required intervention were characteristic of the natural progression of infant botulism (e.g., respiratory arrest). The most frequent SAEs in the BabyBIG® treated group were pneumonia (15%), respiratory arrest (15%), hyponatremia (8%), and anemia (6%). No other SAEs occurred in greater than 5% of BabyBIG®-treated patients.

In the OLS, 285 (97%) patients experienced at least one AE. The most common AEs observed included transiently increased blood pressure (75%), dysphagia (65%), irritability (41%), atelectasis (39%), rhonchi (34%), pallor (28%), loose stools (25%), dermatitis contact (24%), erythematous rash (22%), and vomiting (20%). During BabyBIG® infusion, the most common AEs

observed were a transient increase in blood pressure (50%), irritability (10%), and erythematous rash (6%). The only AE that was considered possibly related to BabyBIG® treatment was the erythematous rash.

There was no evidence of anaphylaxis in any patient enrolled in the OLS. No patient experienced bronchospasm or anaphylactic respiratory arrest, and no patient died during BabyBIG® infusion.

The most common SAEs experienced by the OLS patients during or after treatment were dehydration (10%), lower respiratory tract infection (8%), hyponatremia (6%), and anemia (5%). None of these SAEs were considered related to BabyBIG® treatment, and none required discontinuation of treatment.

Seven deaths occurred in the OLS; 5 of the 7 patients who died were later found not to be infant botulism patients. Two infant botulism patients who received BabyBIG® died. The first received BabyBIG only after irreversible brain damage had occurred from a prior cardiopulmonary arrest. The second received BabyBIG® and recovered from infant botulism, but died subsequently from underlying neuroblastoma. None of the deaths was considered related to BabyBIG® administration.

Table 3 summarizes the occurrence of the only AE considered possibly related to treatment, erythematous rash. In this table, the occurrence of erythematous rash is summarized by day of study relative to day of treatment.

Table 3. Summary of Occurrence of Erythematous Rash

Day of Study Relative to Treatment Day		RCT		OLS
		Placebo (N=64)	BabyBIG (N=65)	BabyBIG (N=293)
		n (%)		
Day -5		0 (0)	1 (2)	6 (2)
Day -4		2 (3)	1 (2)	5 (2)
Day -3		3 (5)	4 (6)	6 (2)
Day -2		5 (8)	2 (3)	22 (8)
Day -1		4 (6)	11 (17)	28 (10)
Day 0*	Before†	5 (8)	9 (14)	32 (11)
	During & After†	2 (3)	9 (14)	39 (13)
Day +1		2 (3)	1 (2)	18 (6)
Day +2		1 (2)	2 (3)	13 (4)
Day +3		3 (5)	0 (0)	7 (2)
Day +4		1 (2)	2 (3)	11 (4)
Day +5		2 (3)	0 (0)	5 (2)

* Day 0 is the day of treatment.
† In reference to treatment

C. Efficacy

In the RCT, the efficacy-evaluable population included the 122 patients with laboratory-confirmed infant botulism. Seven patients were not laboratory-confirmed as having infant botulism were excluded from the efficacy analyses. Of the evaluable population, 59 received BabyBIG® and 63 received placebo. For the primary efficacy variable, length of hospital stay, treatment with BabyBIG® shortened mean hospital stay of all (type A and type B) infant botulism patients by 3.1 weeks, from 5.7 to 2.6 weeks ($p < 0.0001$, t-test). Length of hospital stay was also significantly different when compared by using the K-S test ($p < 0.0001$). For the five secondary efficacy variables, treatment with BabyBIG® significantly shortened length of ICU stay ($p < 0.01$, t-test), duration of mechanical ventilation ($p = 0.001$, t-test), length of tube feedings ($p = 0.001$, t-test), and mean number of AEs per patient ($p = 0.05$, t-test). In addition, treatment with BabyBIG® significantly reduced mean hospital costs ($p < 0.001$, t-test). All of the secondary efficacy results were also significantly different when compared by using the K-S test.

On the basis of these results, it was concluded that BabyBIG®, when used within 3 days of hospital admission, significantly shortens mean hospital stay and is an effective treatment for infant botulism caused by either type A or type B botulinum toxin.

For the OLS, the efficacy-evaluable population included 134 patients with laboratory-confirmed infant botulism. The mean length of hospital stay was the primary and only efficacy variable for the open label studies. For the 134 evaluable infant botulism patients treated with BabyBIG®, the mean length of stay was 2.3 weeks.

IX. Orphan Drug Consideration

BabyBIG® (under the name human Botulism Immune Globulin) was designated as an orphan product for the treatment of infant botulism on 31 January 1989.

X. Marketing History

BabyBIG® has not been commercially marketed.

XI. FDA Decision

The Food and Drug Administration concluded that BabyBIG®, manufactured by the California Department of Health Services, is safe and effective for its intended use based upon the data submitted by the sponsor. An approval letter was issued to the California Department of Health Services on DD MMM 2003.